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# THE MEDICAL CLINICS of NORTH AMERICA

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Volume 26

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## SYMPOSIUM ON ENDOCRINOLOGY

### INTRODUCTION

THE contributors to this number of the *Medical Clinics of North America* are faculty members of the various medical colleges in the medical center of Philadelphia and are actively engaged in the teaching of special or general endocrinology, and in the clinical practice of endocrinology. They are thus individually competent to respond to a request to embody in their text practical and authoritative material to guide the general practitioner in the diagnosis and treatment of endocrine disorders.

World War II has taken, and will continue to take, many specialists in this and other fields of medicine. It is, therefore, an opportune time for these authors to write of their experiences and therapeutic conclusions in the field of clinical endocrinology—a field in which the rapidity of scientific and therapeutic advances is unparalleled—and to discuss the factors which have successfully guided them.

It is our opinion as co-editor that the authors have capably and effectively presented the type of discussion of the various endocrine disorders desired by the general practitioner, and that both he and the specialist will find in the text wisdom born of practical experience. The articles on thyroid and pituitary disorders are particularly noteworthy in this respect, since these disorders engage the interest and cooperation of workers in numerous fields of investigation. The articles on ovarian disorders set forth the paths of study to be pursued in arriving at a competent diagnosis. The underlying prin-

ciples of endocrine therapy for ovarian disorders are given on a physiological and practical basis. In the discussion of the endocrine phases of ovarian disorders the authors remain fully cognizant of the important fact that a patient "is not wholly composed of selected endocrine glands." The complicated problem of the thymus in clinical medicine has not been avoided in this symposium.

It is with pleasure, therefore, that I acknowledge the efforts and cooperation of my co-authors and the W. B. Saunders Company in bringing to press this *Symposium on Endocrinology*.

CHARLES W. DUNN, M.D.

## DIAGNOSIS AND TREATMENT OF PITUITARY GLAND DISORDERS\*

MICHAEL G. WOHL, M.D.†

and

EDWARD LARSON, Ph.D.‡

Of all the endocrine glands, the pituitary body has maintained its prestige as the "master gland." It has a widespread influence on tissues, and by its interrelationship with other parts of the endocrine and the vegetative nervous system, it aids materially in maintaining the physiologic homeostasis of the body.

It is not our purpose to give a comprehensive discussion of the pituitary body and its various hormones, but rather to discuss its disorders, and the possible clinical use of pituitary preparations.

*Anatomy.*—The pituitary gland is made up of:

1. The anterior lobe or the adenohypophysis
2. The posterior lobe (pars nervosa and pars intermedia)
3. The infundibular stalk which connects the pituitary gland with the hypothalamic region

Although the secretions of the anterior lobe are more varied in function than the posterior, the posterior lobe preparations are more adequately standardized and are commercially available to the practicing physician.

### POSTERIOR LOBE

The posterior lobe of the pituitary is made up chiefly of neuroglial cells, pituicytes and nerve fibers. The flow of

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water through the kidneys is regulated by an antidiuretic hormone that is secreted in the posterior pituitary. When the tract of fibers between the hypothalamus and the posterior pituitary is interrupted, there results an absence of the antidiuretic hormone and diabetes insipidus ensues.

### Diabetes Insipidus

Diabetes insipidus can be caused by destruction of the posterior lobe, cutting the hypophysial stalk or by interrupting the supraoptico-hypophysial tract which induces degenerative changes in the pars nervosa. The antidiuretic principle secreted by the posterior pituitary acts directly on the kidney causing reabsorption of water from the tubular fluid.

The chloride excretion in diabetes insipidus is within normal limits and the administration of solution of posterior pituitary does not alter significantly either the serum chloride or urine chloride.

The *diagnosis* of diabetes insipidus usually presents no difficulty. To differentiate it from polyuria due to nervousness, Ryneerson and Kepler<sup>1</sup> recommend the study of the ability of the kidney to concentrate urine. The patient refrains from drinking fluids for twelve hours, whereupon the specific gravity of the last specimen of urine passed during this interval is measured. The patient with *diabetes insipidus* cannot concentrate urine to a specific gravity of more than 1.010 regardless of the abstinence from fluids.

Individuals with polyuria due to nervousness concentrate the urine normally. The differentiation of the polyuria of diabetes insipidus from that of chronic glomerular nephritis is made by the absence in the former of elevated blood pressure, of changes in the blood vessels of the retina and of enlargement of the heart, and lack of increase in the nitrogenous waste products in the blood.

*Treatment of Polyuria and Polydipsia.*—The polyuria and polydipsia of diabetes insipidus are best controlled by the administration of the *solution of posterior pituitary* containing the antidiuretic principle *pitressin*. However, it does not cure the disease. The average dose is 0.5 to 1 cc. given

hypodermically from one to four times daily. It may also be used by the nasal route, either in the form of a tampon of absorbent cotton saturated with 0.5 to 1 cc. of the solution and inserted into one of the nostrils, or in the form of minute amounts of dried posterior pituitary powder used as a snuff.

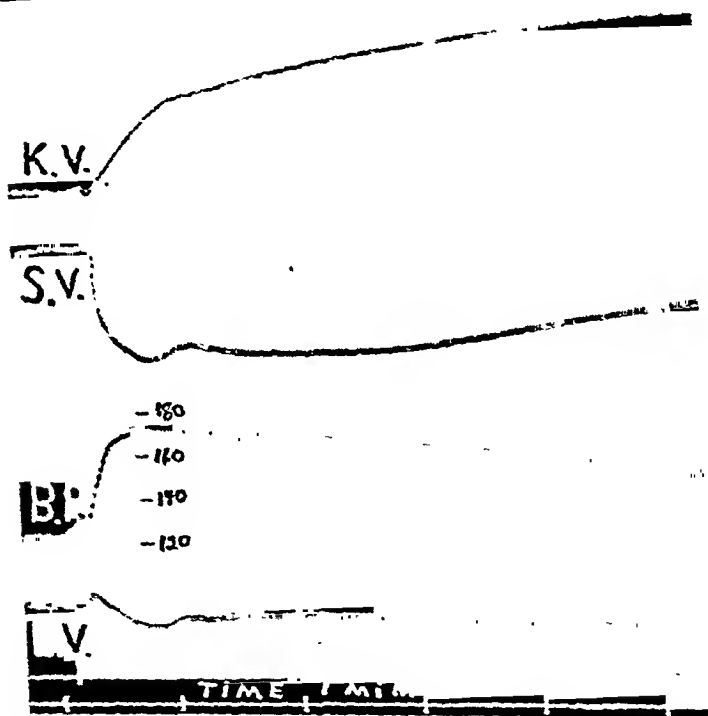


Fig. 208.—The effect of injecting intravenously 0.2 cc. of a solution of posterior pituitary per kilogram into a cat anesthetized with barbital-ether.

L.V. = leg volume, showing slight decrease

B.P. = blood pressure, sustained increase

S.V. = spleen volume, sustained decrease

K.V. = kidney volume, sustained increase

Greene and January<sup>2</sup> have reported on the use of *pitressin tannate in oil*, 5 to 10 pressor units administered intramuscularly in five cases of diabetes insipidus, in which the anti-diuretic effect lasted from thirty to eighty-two hours. There were no disagreeable side effects and the urea clearance and



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## ANTERIOR LOBE

The anterior lobe of the pituitary is made up chiefly of columns of cellular elements and very little connective tissue. Three distinct types of cells are differentiated according to their staining reactions: chromophile (eosinophile and basophile) and chromophobe.

1. Cells having a cytoplasm which is distinctly granular and which reacts to dyes, the so-called *chromophile* cells. (Some of the chromophile cells have an affinity for acid stains, hence are called *acidophile* or *eosinophile* cells.)
2. The *basophilic* cells, which possess the affinity for basic dyes
3. Cells possessing a finely granular nonstaining cytoplasm, the *neutrophilic* or *chromophobe* cells

A great deal of investigation has been conducted on the physiology of the anterior lobe of the pituitary. Its manifold activities have been shown to depend upon the secretion of the various hormones by the cells of the anterior pituitary.

## Hormones of the Anterior Pituitary

The chromophobe cell is generally thought to be without secretory function. The growth principle (somatotropic) is elaborated by the eosinophiles, the gonadotropic principles are elaborated by the basophile cells. There are other principles elaborated by the anterior pituitary lobe. They are the thyrotropic, adrenotropic (corticotropic), lactogenic and diabetogenic. The cell that is responsible for their elaboration is not known with certainty.

For practical purposes, it is to be emphasized that at the present time the anterior pituitary hormones have not been isolated in pure form for clinical use. At best they are (with the exception of the lactogenic hormone) mixtures of several of the active principles—"pituitary soup" as one author called it. It is also to be borne in mind that because of their protein nature, they deteriorate in solution rather rapidly. There are essential differences between the hormones of the anterior and posterior lobe of the pituitary.<sup>3</sup> The anterior lobe preparations exert their characteristic effects relatively slowly, require repeated administrations, and affect primarily the structural elements of the body (e.g., the promotion of

blood pressure were not appreciably altered. Thus, pitressin tannate for its prolonged activity may prove to be superior to the aqueous solution and bring about prolonged comfort to the patient. In some patients, a smaller dosage may prove satisfactory. Pitressin tannate should never be given intravenously; the intramuscular route is to be used.

#### Other Clinical Uses of Posterior Pituitary Preparations

*Pitressin* also elevates blood pressure by contraction of the peripheral blood vessels. The rise in blood pressure is more gradual, it lasts longer, and is not as great as that resulting from the administration of epinephrine. Pitressin is, therefore, of value in postoperative shock and collapse. It should be given subcutaneously or intramuscularly. In patients with coronary thrombosis, when dental work is required, the local anesthetic should be combined with pitressin rather than with epinephrine for evident reasons. Pitressin also stimulates the musculature of the intestine, thus increasing peristalsis. In intestinal atony following extensive abdominal operations, and in flatulence during pneumonia, the use of pitressin has proved valuable. Since the introduction of prostigmine, however, the use of pitressin is not resorted to for abdominal distention as often as formerly. (See Fig. 208.)

Another principle of the posterior pituitary is the oxytocic factor *pitocin*. It causes contraction of the uterine muscle following labor. Because of this property, its use in obstetrics is well known to the practicing physician.

#### COMMON PREPARATIONS OF THE POSTERIOR PITUITARY

*Solution of Posterior Pituitary*, U.S.P. XI. One cc. contains 10 oxytocic units. These are the water-soluble constituents from the posterior lobe. This strength is sometimes labeled "Obstetrical" and another of twice the strength is labeled "Surgical." Because some manufacturers use the blood pressure method of standardization, and also because pitressin has been prepared and standardized using posterior pituitary as a basis, it can also be said that the obstetrical contains 10 pressor units and the surgical, 20 units.

*Posterior Pituitary*, U.S.P. XI. The dried and powdered posterior lobe.

*Ampoules of Pitocin*, N.N.R. The separated oxytocic principle of the posterior pituitary standardized so that each cubic centimeter contains 10 oxytocic units.

*Ampoules of Pitressin*, N.N.R. The separated pressor principle of the posterior pituitary standardized so that each cubic centimeter contains 20 pressor units.

given these preparations should be kept under constant observation, since precocious puberty with marked hypertrophy of the genitalia may occur; treatment should be discontinued before genital growth becomes excessive.

It is to be stressed that before undertaking treatment of an undersized child, the possibility of a cyst or neoplasm in or near the anterior pituitary should be excluded. It is also to be borne in mind that nonendocrine causes of retardation of growth, such as congenital syphilis, juvenile tuberculosis, congenital heart disease, faulty nutrition, renal rickets and other medical conditions should receive attention before endocrine therapy is planned.

*Gonadotropic Hormones.*—At present, it is believed that there is a follicle-stimulating hormone (F.S.H.) and luteinizing hormone (L.H.). The luteinizing principle also stimulates the interstitial cells of the testes and produces growth and development of the accessory sex glands in the male.

Van Dyke and his collaborators<sup>9</sup> have made progress in isolating the follicle-stimulating and luteinizing principles in pure form. Their work, however, awaits further experimental confirmation and application in the clinic.

*Thyrotropic Principle.*—Loeb, Aron and others<sup>10</sup> have definitely established the relationship of the anterior pituitary lobe to the thyroid gland. However, the thyrotropic extract of the anterior pituitary is of limited clinical value. In our practice, we should still continue to use desiccated thyroid in cases of hypothyroidism, in preference to the thyrotropic extract. Recently, cases have come to light of myxedema due to absence of the thyrotropic hormone as a result of hypofunction of the anterior pituitary.<sup>11</sup> The "pituitary type" of myxedema is associated with adrenocortical insufficiency (hypotension) and absence of diabetogenic and follicle-stimulating substances (hypoglycemia, amenorrhea, loss of libido). It is important to bear in mind that in "pituitary myxedema," thyroid administration produces no improvement and may cause vomiting, marked abdominal pain and collapse. The unfavorable response to thyroid in a suspected case of myxedema should make one suspicious of its pituitary origin (Fig. 209).

growth). The posterior lobe extracts, on the other hand, elicit an immediate pharmacodynamic response on either isolated tissue preparations (e.g., the uterus) or in the intact animal.

*Growth Principle.*—The growth principle appears to influence skeletal growth mainly by stimulating the epiphyseal cartilages.<sup>4</sup> The commercial products representing the growth principle are impure. In addition to the growth principle, they contain a certain amount of gonadotropic and thyrotropic, and, possibly, adrenotropic principles; they are also high in protein. They are water-soluble, and their effects are not sustained.

Evans and his associates<sup>5</sup> have recently freed the growth factor from contamination with lactogenic and thyrotropic hormones. The effect of this growth hormone in animals can be observed by the "silver nitrate" line of the epiphysis forty-eight hours after its administration. The growth hormone causes retention of proteins in the body, an overgrowth in a normal animal or a normal growth in a hypophysectomized animal without any effect on the so-called target organs (organs affected by other pituitary hormones: adrenal, thyroid, ovaries, etc.). To our knowledge this hormone is not available for human use. Many factors are concerned in the process of growth, such as heredity, environmental conditions, proper nutrition and influence of several of the other endocrine glands. Some workers<sup>6</sup> have reported resumption of growth following treatment with pituitary extracts in children who ceased growing. However, the possibility of spontaneous growth has not been excluded, and again, these "successfully" treated children have not reached the stature desired for the age. My personal experience with pituitary growth promoting extracts has been disappointing.

Recently, attention has been called to the fact that acceleration of growth in undersized children can be obtained by the administration of *chorionic gonadotropins* and *testosterone propionate*.<sup>7, 8</sup> Since at present there is no commercial pituitary growth hormone available, the use of chorionic gonadotropins (pregnancy urine) and the male sex hormone offers a means of stimulating growth. The patient who is

However, valuable as these observations are, they cannot, at present, be utilized in clinical medicine. The work of Young<sup>15</sup> is interesting in this connection. He succeeded in establishing a permanent diabetic state in dogs by damaging the islands of Langerhans, through the injection of crude extracts of the anterior pituitary lobe. It is thought that the altered carbohydrate metabolism is mediated by "a biochemical system in the liver, the equilibrium of which is governed by the opposing forces of the pancreas on the one hand and of the anterior pituitary, thyroid and adrenal cortex, on the other."<sup>15a</sup>

Although the existence of a definite type of diabetes induced by overactivity of the anterior pituitary gland is now recognized, treatment of diabetes mellitus by irradiation of the pituitary gland has yielded most inconclusive results. The same may be said about the use of estrogenic substances as an adjunct in the treatment of diabetes mellitus. Until more is learned about this interesting phase of carbohydrate metabolism, the physician should continue to rely on insulin and diet for the control of diabetes.

#### HYPOPITUITARISM

From a clinical point of view, pituitary disorders are divided into two opposed groups—those due to glandular overfunction (hyperpituitarism) and those due to glandular underfunction (hypopituitarism). The chief pathologic processes involving the pituitary gland are: adenomas and other neoplastic processes, functional hypoplasia, hyperplasia and destructive lesions. The destructive lesions of clinical importance are tuberculosis, congenital or acquired syphilis, and necrosis due to emboli and thrombi. Impaired function of the anterior pituitary may result from the acute infectious diseases of childhood. Hypopituitarism in the female may develop at the onset of menstruation, menopause, or following pregnancy (Fig. 210). Doubtless, during these epochs, there is an increase in the pituitary secretion which may be followed by pituitary exhaustion. An analogous situation during the menstrual epoch may occur with regard to the thyroid gland.

*Lactogenic Hormone.*—This hormone is the only pituitary hormone that has been obtained in crystalline form.<sup>12</sup> It has been used in nursing mothers who did not lactate sufficiently. However, the increase in lactation was nil or negligible.<sup>13</sup>

*Adrenotropic Hormone.*—The concept of relationship of the anterior lobe of the pituitary to the adrenal cortex is supported by considerable experimental evidence. Clinically this is borne out by the great similarity in appearance of patients with basophilic adenoma and adrenal cortical tumor. For the

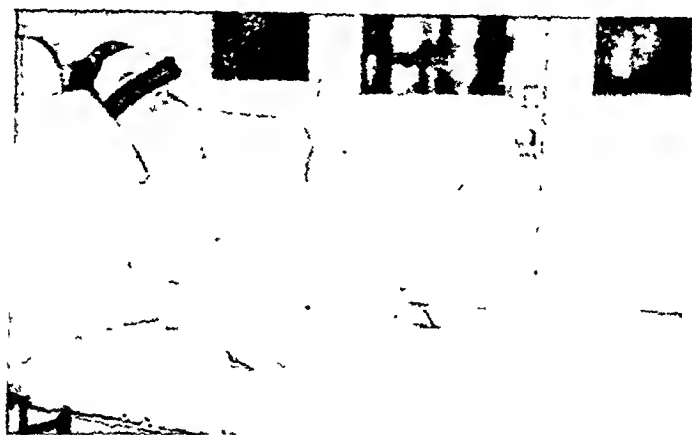
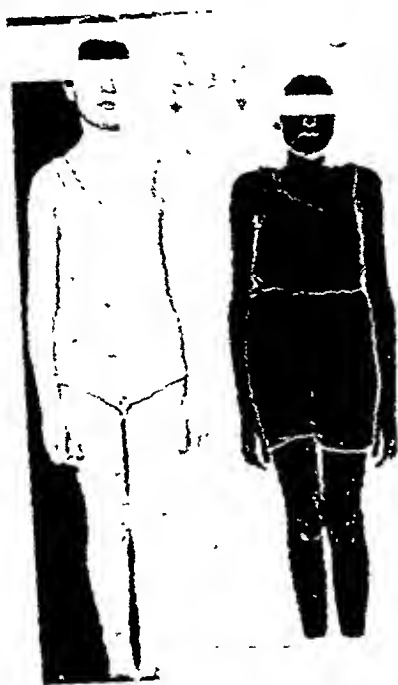


Fig. 209.—Pituitary myxedema in a man aged sixty years, who complains of attacks of faintness, sweating and loss of consciousness. B.M.R. —45 per cent. Blood cholesterol 172 mg. per 100 cc. Blood pressure 80/50. Bradycardia. Patient is extremely sensitive to insulin. Absence of axillary and pubic hair. Responds poorly to thyroid therapy. Case will be described in detail elsewhere by Dr. Kramer. (Service of Dr. David Kramer, Philadelphia General Hospital.)

present, the adrenotropic extract of anterior pituitary is far removed from immediate application in human therapy.

*Diabetogenic Principle.*—There is adequate evidence to support the view that the pituitary lobe contains a principle which has a definite effect on carbohydrate metabolism and also on fat and protein metabolism. In the last four years, Houssay, Long and Lukens<sup>14</sup> have made important contributions on the interrelationship between the pituitary and the adrenal cortex in the metabolism of carbohydrates and fats.

chlorides are low and there is an increase in concentration of chloride in the urine.<sup>17\*</sup> X-ray of the cranium may reveal absence of cancellous bone formation with rudimentary development of paranasal sinuses (pituitary infantilism). The sella turcica may be small in size. In the presence of an intra-



A

B

Fig. 211.—Pituitary dwarfism in a girl (B), aged fourteen years. Height 53 inches, weight 57 pounds. Compare with her sister (A), aged nine years.

sellar expanding tumor, the sella turcica may be distorted and erosion of the clinoid processes is noted. The visual fields may be constricted and the optic chiasm implicated.

Before undertaking any therapy for hypopituitarism, an intrasellar or suprasellar tumor should be ruled out. All too often have patients come to an endocrine clinic for dwarfism

\* The Coulter, Power and Wilder chloride depletion test is used for determining the latter (*J.A.M.A.*, *III*: 117, 1938).



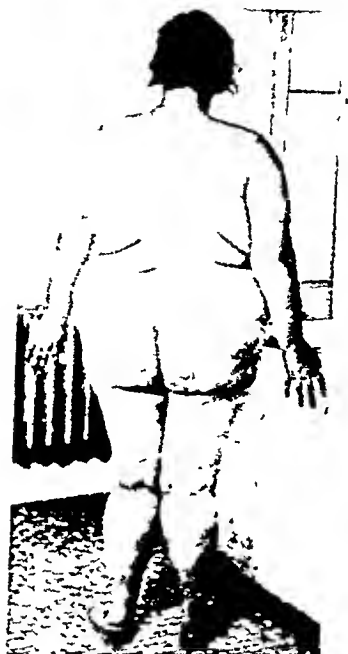


Fig. 210.—Rapid gain in weight following two pregnancies in a woman aged thirty-four years; menstruation has become irregular and scant.

### Clinical Diagnosis of Hypopituitarism

The clinical diagnosis of hypopituitarism rests upon three factors: (1) Elicitation of the etiologic factors. (2) Observance of the various manifestations in the target organs: skeletal undergrowth, genital underdevelopment, and disturbed menstruation in the female (irregularity, scantiness or amenorrhea, and loss of libido in the male); hypotension is seen more frequently than hypertension. The patient has a soft skin with girdle type of adiposity; there is sparse growth of hair; the upper measurements are usually greater than the lower.\* (3) Laboratory findings: a normal or low basal metabolic rate, decreased specific dynamic action of protein;<sup>16</sup> the blood cholesterol is within normal range; there is a tendency toward a low blood sugar level (craving for sweets) and increased sugar tolerance. The blood and urine are low in pituitary gonadotropins. The blood and serum

\* Upper measurement is the length from the vertex to symphysis pubis; lower measurement is from the symphysis pubis to the bottom of the heel,

usually not below the average and the patient is overweight. Pituitary infantilism is probably due to an inherited under-functioning of the eosinophile elements of the anterior pituitary lobe. The Lorain-Levi type of dwarfism is characterized by a diminution of all parts of the body; however, the infantile proportions are retained. Such patients are not mentally retarded. It is in this type of dwarfism that various pituitary growth extracts have been used. However, there is no record in the medical literature of any case in which the evidence could be presented as conclusive of accelerated growth following such therapy.

### Fröhlich's Syndrome

Fröhlich's syndrome, or *dystrophia adiposogenitalis*, may become apparent in childhood, adolescence or maturity. If the disease begins in early childhood, there may be retarded skeletal development, obesity, and the external genitalia are small and remain infantile. In the male the testes may fail to descend. It is in such patients with undescended testes that chorionic gonadotropin may prove effective in bringing the testicles down into the scrotum. In the female, there is genital atrophy, and the uterus and ovaries are small. The secondary sex characteristics are partially developed and menstruation is delayed until from fifteen to eighteen years of age. The obesity is most marked at the shoulders, breasts, lower abdomen, hips and thighs. The arms and legs are rather thin (Figs. 213 and 214). In this connection, it should be stated that the laity and the physician should realize that obesity in childhood demands inquiry, and if it is found to be pathologic, treatment should be instituted at the time when there is still some chance of success. In the adolescent form of Fröhlich's syndrome, there may be skeletal overgrowth, the size of the genitalia may be normal, but the secondary sex characteristics are absent; in girls, menstruation may be delayed. Fröhlich's syndrome after the age of thirty or forty years is evidenced by obesity, menstrual disturbances, and frequently hypertrichosis of the face, arms and thighs. In the majority of patients with Fröhlich's syndrome, there is no clinical evidence of "neighborhood pressure signs," and the x-ray of the

- or pituitary amenorrhea after having received "injections," prior to admission, only to reveal a progressive tumor involving the optic nerves. Not in all instances of hypopituitarism does one find manifestations of hyposecretion of all the hormones; more often hypopituitarism may manifest itself by hyposecretion of one or two of the pituitary principles.

### Pituitary Infantilism

Pituitary infantilism may result from pure hypoplasia of the anterior lobe, or from hypoplasia caused by tumor pressure. Infantilism is characterized by a general arrest of skeletal



Fig. 212.—Pituitary dwarfism and progeria in a boy aged fourteen years.

growth and an underdevelopment of all organs and systems of the body, however, without adiposity. Such persons never develop sexual maturity, nor associated secondary sex characteristics (Figs. 211 and 212). This condition is not to be confused with the Fröhlich syndrome, in which the height is

usually not below the average and the patient is overweight. Pituitary infantilism is probably due to an inherited under-functioning of the eosinophile elements of the anterior pituitary lobe. The Lorain-Levi type of dwarfism is characterized by a diminution of all parts of the body; however, the infantile proportions are retained. Such patients are not mentally retarded. It is in this type of dwarfism that various pituitary growth extracts have been used. However, there is no record in the medical literature of any case in which the evidence could be presented as conclusive of accelerated growth following such therapy.

### Fröhlich's Syndrome

Fröhlich's syndrome, or *dystrophia adiposogenitalis*, may become apparent in childhood, adolescence or maturity. If the disease begins in early childhood, there may be retarded skeletal development, obesity, and the external genitalia are small and remain infantile. In the male the testes may fail to descend. It is in such patients with undescended testes that chorionic gonadotropin may prove effective in bringing the testicles down into the scrotum. In the female, there is genital atrophy, and the uterus and ovaries are small. The secondary sex characteristics are partially developed and menstruation is delayed until from fifteen to eighteen years of age. The obesity is most marked at the shoulders, breasts, lower abdomen, hips and thighs. The arms and legs are rather thin (Figs. 213 and 214). In this connection, it should be stated that the laity and the physician should realize that obesity in childhood demands inquiry, and if it is found to be pathologic, treatment should be instituted at the time when there is still some chance of success. In the adolescent form of Fröhlich's syndrome, there may be skeletal overgrowth, the size of the genitalia may be normal, but the secondary sex characteristics are absent; in girls, menstruation may be delayed. Fröhlich's syndrome after the age of thirty or forty years is evidenced by obesity, menstrual disturbances, and frequently hypertrichosis of the face, arms and thighs. In the majority of patients with Fröhlich's syndrome, there is no clinical evidence of "neighborhood pressure signs," and the x-ray of the

sella turcica is normal. Recent studies incline to the view that Fröhlich's syndrome is caused by a lesion in the hypothalamus rather than by primary disease or dysfunction of the pituitary gland.

*Treatment.*—An occasional case of pre-adolescent Fröhlich's syndrome "straightens out" spontaneously without treatment. However, this rare occurrence should not preclude the institution of early treatment. The treatment includes



Fig. 213.—Pre-adult hypopituitarism in a girl aged thirteen years.

measures designed to correct obesity, to stimulate gonadal development, and to relieve amenorrhea and hypertrichosis in the female patient. For the obesity, a subcaloric diet, high in proteins, in vitamins and in calcium is of major importance. Small doses of desiccated thyroid are beneficial in the reduction regimen, and in stimulating pituitary function. For hypogonitalism in the male patient chorionic gonadotropin (A.P.L.), 200 rat units three times weekly, may be employed.

The restoration of menstrual periodicity in girls with Fröhlich's syndrome is very difficult. The combined use of diet, low dosage irradiation of the pituitary gland and ovaries and the administration of estrogenic and pituitary extracts are recommended by Mazer and Israel.<sup>18</sup> For hypertrichosis, electrolysis is the treatment of choice. It is obvious that with alteration of the visual fields and other evidence of a tumor or cyst, surgery is recommended.



Fig. 21<sup>2</sup>—Hypopituitarism in a girl aged twenty years. Sella turcica is smaller than the average. X-ray of skeleton reveals that the patient is markedly retarded in closure of epiphyseal lines. In general, she shows a bone age of somewhat less than fourteen years. Primary amenorrhea failed to respond to various endocrine therapy.

#### Psychic and Personality Changes in Hypopituitarism

Lurie<sup>19</sup> has recently stressed the psychic manifestations and personality changes observed in hypopituitarism. Children with Fröhlich's syndrome lack aggressiveness; "they are shy, gentle, easy-going, timid and artistic." On the other hand,

sella turcica is normal. Recent studies incline to the view that Fröhlich's syndrome is caused by a lesion in the hypothalamus rather than by primary disease or dysfunction of the pituitary gland.

*Treatment.*—An occasional case of pre-adolescent Fröhlich's syndrome "straightens out" spontaneously without treatment. However, this rare occurrence should not preclude the institution of early treatment. The treatment includes



Fig. 213.—Pre-adult hypopituitarism in a girl aged thirteen years.

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rhea, and psychic changes, premature senility, loss of libido, and potentia. The symptoms usually follow postpartum hemorrhage and collapse. Anorexia nervosa may mimic Simmonds' disease and presents difficulties in the differential diagnosis. Severe loss of weight and a low basal metabolic rate in a young unmarried woman who has never been pregnant favor the diagnosis of anorexia nervosa. A decided improvement of

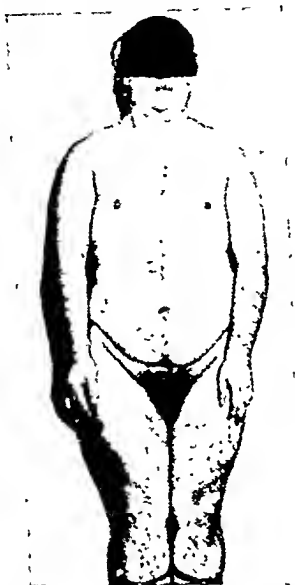


Fig. 216.—Fröhlich dystrophy in a man aged twenty-two years. Timid, submissive, completely withdrawn into himself.

a return to normal health as a result of psychotherapy or after any treatment available at present (including endocrine therapy) further suggests the diagnosis of anorexia nervosa.<sup>20</sup>

CASE REPORT (Fig. 216a).—A. M. was a single, white woman of twenty-five years.

*Clinical Data.*—Progressive loss of weight from 1931 to 1933 (140 to 68 pounds). Abdominal pain, appendectomy January, 1933. Amenorrhea since 1933. Progressive weakness, headache, depression, atrophy of breasts, edema of eyelids and lower extremities, dizziness, loss of hair, dry cold skin, amnesia spells, pulse rate 54 to 60. Hypotension, with blood pressure 70 to 90 mm. systolic, 50 to 45 mm. diastolic. Atrophy of the uterus, sub-normal temperature.



children of the Lorain-Levi type of dwarfism are mentally alert, forward and aggressive. Depending largely upon the environment, the timid child may overcompensate and become aggressive, antisocial and delinquent (Fig. 215); or the child may become more timid and refuse to make normal social contacts (Fig. 216). In view of the frequency of these behavior difficulties, both the physician and the parents

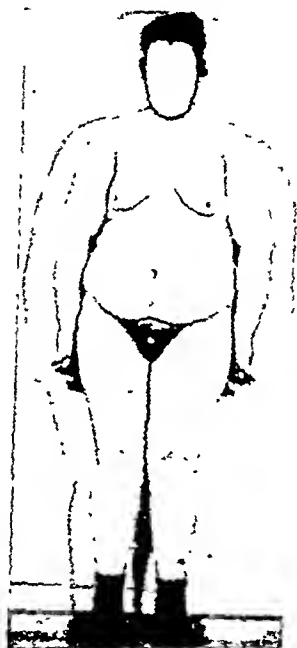


Fig. 215.—Fröhlich dystrophy in a boy aged sixteen years. Aggressive, anti-social, given to stealing money from his mother in order to buy sweets.

should make every effort to correct the condition early and thus prevent the development of personality maladjustments.

#### Simmonds' Disease

The term Simmonds' disease, or *pituitary cachexia*, is to be applied to patients in whom there has been extensive destruction or atrophy of the pituitary gland. The condition is rare. The outstanding *clinical features* of the disease are extreme emaciation, weakness, falling out of teeth and hair, amenor-

90 and 100 mm. of mercury. Collip fraction was substituted for anterior pituitary liquid to raise the basal metabolic rate. The patient subsequently went into acute coma. Blood sugar readings of 18 to 20 mg. per 100 cc. of blood were obtained. Glucose was given intravenously; adrenalin was ineffective.

*Autopsy.*—General osteoporosis of skull, peritoneal fluid moderate in amount, fatty tissue absent. *Endocrine:* Pituitary—marked atrophy, being 50 per cent of normal in size, with microscopic, diffuse atrophy, some fibrosis, and loss of cytoplasm from cells. Parathyroid—"very unusual picture" made up of "dark chief cells" which is opposite of adult normal. Pancreas—large size, microscopically normal. Thyroid—normal resting of gland with increase in the stroma of a dense fibrous character. (Thyrotropic fraction given.) Suprarenal—microscopically normal. (Adrenotropic fraction given.)

### HYPERPITUITARISM

Hyperplasia of the eosinophile cells may result in *gigantism* when the disease begins at an age when the epiphyses are

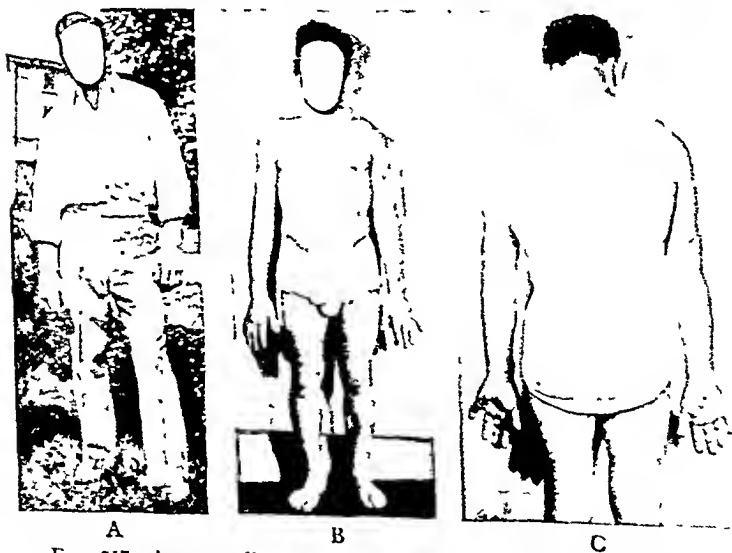


Fig. 217.—Acromegalic gigantism in a man aged twenty-eight years, which began with unusual rapidity of growth at the age of fifteen. *A*, At the age of twenty years. Physically powerful; uncontrolled libido. *B*, At the age of twenty-eight years. Loss of former strength; extremely tired; decreased libido. Hypotension. *C*, Marked bowing of spine. Sella turcica is expanded. Slight erosion of clinoid processes.

ununited, or *acromegaly* when it begins in postadolescence. The disease is protean in manifestations, but rare in occur-

*Laboratory Data.*—Basal metabolic rate, minus 44. Wassermann and Kahn—negative. Blood per 100 cc.: calcium, 10.4 mg.; phosphorus, 4 mg.; chlorides, 496 mg.

*Sugar Tolerance Curve*

	Fasting	$\frac{1}{2}$ hour	1 hour	2 hours	3 hours	
50 Blood gm. Urine	82 0	149 0	176 0	164 plus	180 0	mg. Sugar
100 Blood gm. Urine	82	172	200	183	65	mg. Sugar

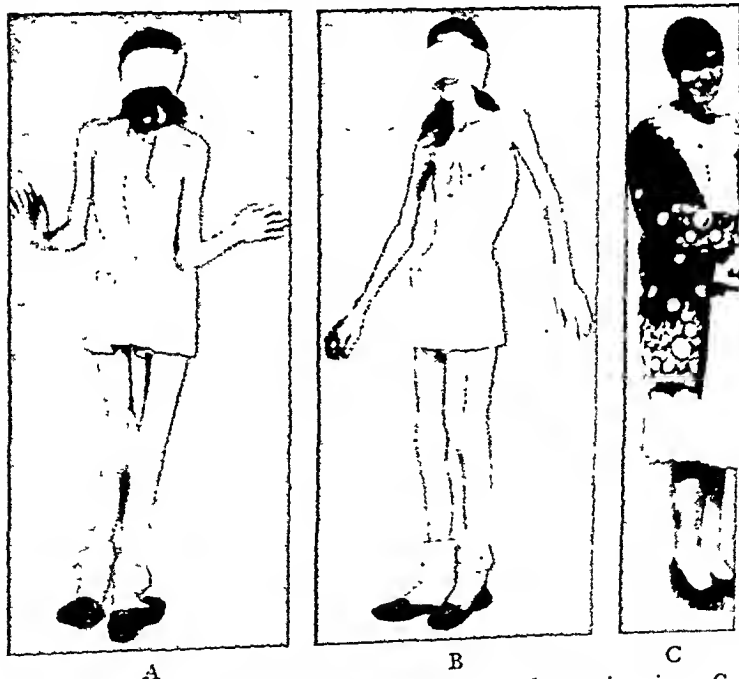


Fig. 216a.—Simmonds' disease. *A* and *B*, Anterior and posterior views. *C*, Prior to onset of illness. (See Case Report.)

*Therapy.*—Anterior pituitary, 2 cc. daily; progynon B, 10,000 R.U. every fifth day. Menstruation (first in thirty-four months) occurred at end of fifty-three days. Total dosage: progynon B, 100,000 R.U. Anterior pituitary liquid (Armour) (92 cc.) was administered. The thyroid, uterus and breasts increased in size and systolic blood pressure rose to between

In conclusion, some results with posterior pituitary lobe hormones have been spectacular in the experimental animal. However, the clinical application of these findings is difficult



Fig. 219.—Obesity following an attack of encephalitis lethargica in a woman aged thirty-five years. Patient gained 100 pounds in nine months after the attack. Present weight 314 pounds.

to evaluate because (1) of the paucity of pure preparations and (2) so many of the anterior pituitary lobe disturbances are not well defined in the clinic.

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rence. The hyperpituitary state may gradually change into a hypopituitary state with symptoms of asthenia, hypotension and loss of libido (Fig. 217). The treatment of gigantism and acromegaly is at best unsatisfactory. This phase of the pituitary and its neoplastic processes was considered elsewhere.<sup>21</sup>

### Cerebral Obesity

Extreme obesity may result from lesions in the region of the pituitary, infundibulum, or paraventricular nuclei in the floor of the third ventricle. Usually this type of obesity is associated with symptoms of diabetes insipidus (Fig. 218).



Fig. 218.—Cerebral obesity in a man aged thirty-eight years. Height 67 inches, weight 291 pounds. Gained 100 pounds in twelve months; with increase in weight developed drowsiness, polyuria, and marked retention of sodium chloride. (From author's article in *Am. J. Med. Sc.*, May, 1932, Lea & Febiger.)

Camus and Roussy<sup>22</sup> and more recently Long<sup>23</sup> have shown that extreme obesity in animals may result from hypothalamic injury. In this connection it is interesting to note that cases of obesity may follow epidemic encephalitis (Fig. 219).

## DIAGNOSIS AND TREATMENT OF PITUITARY TUMORS\*

BERNARD J. ALPERS, M.D., Sc.D. (Med.)†

*Definition.*—Primary tumors of the pituitary gland may be defined as those tumors arising from the gland structures and growing within the sella turcica. This excludes, therefore, all tumors arising above the sella turcica (suprasellar) and those lying adjacent to the sella (parasellar).

*Incidence.*—The occurrence of primary tumors of the pituitary varies from 13 to 15 per cent of all types of brain tumor, and probably is closer to the former figure. An incidence of 17.8 per cent is found in Cushing's series, but this is higher than found in other clinics.

### TYPES OF PITUITARY TUMORS

The tumors occupying the pituitary region are made up of the following types: (1) adenomas, (2) hypophyseal stalk tumors, (3) cysts of Rathke's cleft. They arise, therefore, from the substance of the gland, exclusively the anterior lobe portion, from the intermediate portion, and from cells which lie along the infundibular stalk. No known tumors arise from the posterior lobe of the gland.

The vast majority of the primary pituitary tumors are adenomas; the hypophyseal stalk tumors and Rathke cleft cyst represent rare primary types.

The *adenomas* are of three types: (1) chromophobe, (2) eosinophilic, (3) basophilic. They arise from the corresponding cell types of the anterior lobe, the chromophobe from the most numerous of the acinar cells which do not have specific granules within their cytoplasm; the eosinophilic from the eosinophile cells of the anterior lobe; the basophilic

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## CLINICAL FEATURES

Since the pituitary adenomas are by far the most numerous of the primary pituitary tumors, a description of their clinical features will suffice for pituitary tumors.

## History of the Illness

The problem in pituitary tumors is primarily that of headache and failing vision in adults and it is these symptoms of which patients complain most frequently. Pituitary tumors are apt to be found in persons ranging in age from fifteen to sixty years, the greatest age incidence occurring between thirty and sixty. Failing vision is more often the presenting complaint than is headache. Under some circumstances loss of libido and potency in the male, or menstrual disturbances in the female, may be the chief complaint.

*Headache* is present in about three-fourths of cases of pituitary tumor, but it is a first symptom in only one-third of the cases. In about two-thirds the onset is marked by visual complaints which precede the appearance of the headache. The headache or visual symptoms as a rule have been present for a period of several months or one to two years before the patient presents himself for treatment, but symptoms may have been present for several years in some instances before the patient appears for relief. The headache usually is frontal in location, often most intense behind the eyes or in the temples where it may be described as a pressure sensation, and is usually constant. While it is most often frontal in location, it may be generalized not infrequently and in not a few instances it is described as occipital or parietal in location. It may even be unilateral and be mistaken for migraine. It is paroxysmal in some cases, however, and in others may be present for long periods of time, months or years, with sudden cessation of the headache, probably as a result of decompression of the tumor into the sphenoid sinus. In some instances the tumor may run its course without the development of headache at any time.

In the majority of cases *visual complaints* precede headache as the presenting symptom, but both disturbance of vision and headache may appear simultaneously in some instances.



from the basophile cells. The chromophobe adenoma is associated with a hypopituitary endocrine disturbance, the eosinophilic adenoma with acromegaly, and the basophilic adenoma with basophilism or Cushing's syndrome.

The *cyst of Rathke's cleft*, a rare type of tumor, arises from the cell remnants of Rathke's pouch in the embryo. *Hypophyseal stalk tumors* may arise within the sella turcica and remain confined to it. They take their origin from cell rests of the embryonic hypophyseal stalk lying at the junction of the infundibulum and the anterior lobe of the hypophysis just under the diaphragm of the sella turcica.

#### PATHOLOGY

Tumors arising within the pituitary gland produce their symptoms by three mechanisms: (1) expansion of the sella turcica in which the gland lies, (2) compression of the overlying optic nerves and chiasm, (3) destruction of the pituitary gland.

Tumors arising within the pituitary gland cause an enlargement of the sella turcica and usually remain confined to it. They compress the optic nerves and optic chiasm growing in such fashion as to push upward against the chiasm, causing it to straddle the tumor and resulting in flattening and stretching of the optic nerves. While they remain confined to the sella turcica for the most part, some of them may escape into the cranial cavity by extension through the opening for the infundibular stalk in the diaphragm or by rupture of the diaphragm itself. They may extend into the frontal region, into the cavernous sinus region, or spread out between the temporal lobes.

The *adenomas* are soft tumors, usually solid but sometimes cystic. They all respond well to irradiation, the eosinophilic type in particular. Chromophobe adenomas may be malignant in rare instances, growing very rapidly and extending into the skull bones. The *hypophyseal stalk tumor* is an epithelial growth, composed of epithelial cells, usually cystic, and often containing calcium. *Rathke's cleft cyst* is a rare epithelial tumor which is always cystic and is composed of columnar ciliated epithelium.

TABLE I  
FEATURES OF PITUITARY ADENOMAS

Type	Optic Atrophy	Blindness	Deformity of Sella Turcica	Endocrine Disturbances	Hormone Excretion
Chromophobe	1	1	1	Amenorrhea Loss of libido Increased weight Change in skin and hair Increased sugar tolerance Decreased basal metabolism	
Acidophilic	+	1	1	Increased size of hands and feet Prognathism Thickening of skin Increased size of lips and tongue Enlargement of jaw and sinuses	Growth hormone Increased Sex hormone decreased
Basophilic	0	0	0	Vasculitis Hypertension Fat distributed about face, neck, shoulders, abdomen Adrenal purpura Osteoporosis	

The visual disturbance is usually described as a blurring of vision, foggy or misty vision, in one or both eyes. There may be a history of relief of visual symptoms in the past by glasses. This may catch the unwary off guard, since the obvious inference is to conclude that a refractive error is present and to dispose of the case on this basis. In some cases the patient may complain of inability to see out of the corners of the eyes or of colliding with objects on the side, (subjective hemianopsia) thus calling attention to the hemianopsia. This complaint is unusual, however, the field defect either remaining unnoticed by the patient or overlooked in the more obvious visual loss as seen in the dimness of vision. It is not unusual, despite the closeness of the relationship of the tumor growth to the optic nerves and chiasm, to find patients who make no complaint of visual disturbance. The great majority will however call attention to visual loss (blurring vision, loss of eyesight, spots before the eyes) and it is precisely because of this complaint that pituitary tumor must be suspected. Diplopia is at times an early complaint.

In addition to the headache and visual history, there will usually appear a story of *endocrine complaints*. In the male this is outstandingly concerned with loss of libido and sexual potency, failure of development of hair growth, infrequent shaving, and gain in weight. In the female, the most common complaint is disturbance in menstrual function, usually seen as sparsity of flow or even as cessation of menstruation.

Other less common and less specific complaints are found in the not uncommon history of *fatigue* and general *loss of muscular power*. Excessive thirst and urination, unusual desire for sweets, and excessive reaction to cold are other symptoms. In acromegalics a history of excessive growth of the extremities, of change in the appearance of the features, fatigue, and of the need of larger gloves and shoes is often obtained.

The story in summary, therefore, consists of frontal headache of brief or long duration, preceded or accompanied by loss of vision, and amplified by endocrine complaints of various types, depending on the nature of the endocrine disturbance.

The visual field defect begins in the upper temporal quadrant of each eye and proceeds downward in the temporal fields. This type of field cut is found in a high percentage of in-

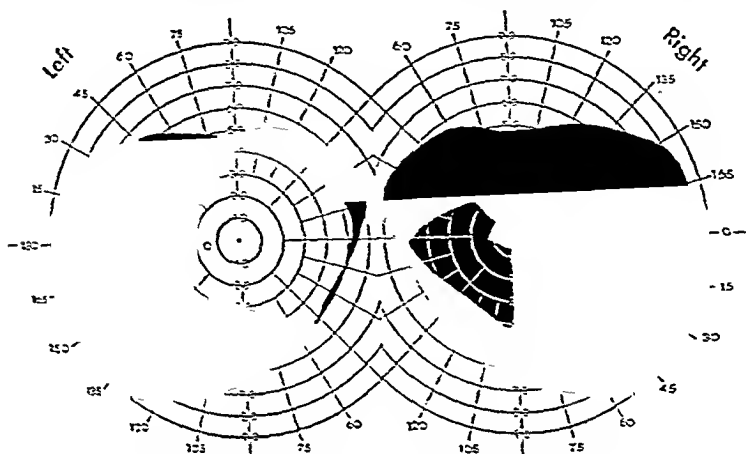


Fig. 220.—Advanced bitemporal hemianopsia in a case with almost complete loss of vision in the right eye.

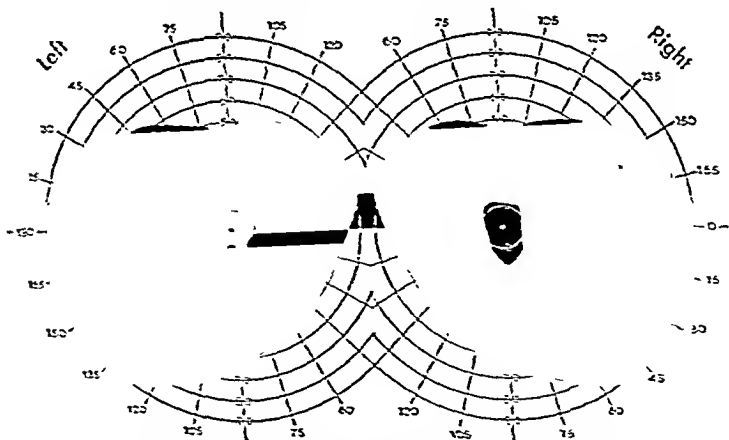


Fig. 221.—Complete loss of visual fields except for central vision in an advanced case with moderately good visual acuity.

stances (75 per cent or more). It is usually present for both form and color fields and is associated with spacing of macular vision. Bitemporal hemianopsia for color may be found

### Objective Findings

With such a history, examination will reveal the following features:

1. OPTIC ATROPHY.—This is the result of pressure of the tumor against the optic nerves as it expands upward, but traction of the nerves and chiasm as well as blockage of vascular supply by the pressure are also factors. It constitutes one of the most important of the signs of pituitary tumors. The change is seen as a primary optic atrophy usually involving both disks, and is present in at least three-fourths of the cases at the time of examination. In some cases the optic atrophy may be unilateral, one eye being normal. The loss of visual acuity is usually proportional to the optic atrophy, but it is not unusual to find cases in which the optic disks are normal (6.5 per cent) while the visual acuity is impaired (6/15 or 6/20 and less). In some cases with optic atrophy there may be surprising retention of visual acuity. The need of recognizing cases early is shown by the fact that in almost all series of cases which have been reported there has been a high percentage of blindness in one or both eyes by the time patients appear for treatment. DeSchweinitz reports the following:

Blind, or near blind, both eyes	15 cases
Blind, or near blind, one eye ...	57 cases
Standard central vision, both eyes	7 cases

In some series of cases about 5 to 6 per cent have been found with a low degree of elevation of the optic disks (1–1.5 diopters). In others no choked disk has been found. Very rarely pituitary adenomas may cause high choked disk. An instance has been recorded of a choked disk as high as 6D without visual field changes. In this case a large accumulation of fluid under the frontal lobes may have contributed to the edema since the pituitary tumor, a cyst, was confined to the sella turcica.

2. HEMIOPHIA.—In typical cases the optic atrophy is associated with *bitemporal hemianopsia* (Fig. 220), due to pressure in the optic chiasm on the fibers from the nasal half of the retina which receive impulses from the temporal fields.

*Scotomas* are found in the visual fields in about 15 per cent of cases. The scotoma is usually central and is most often the result of a retrochiasmal extension of the tumor. In other instances a scotoma may result from anterior extension of the tumor with impingement on an optic nerve.

In cases with advanced optic atrophy and visual loss, visual fields may be impossible to obtain. In other instances there may be blindness of one eye and temporal hemianopsia in the other.

The combination of eye findings varies, therefore, in pituitary tumors. These may be grouped as follows:

- (1) Optic atrophy and bitemporal hemianopsia. This occurs in the majority of instances (75 per cent). The degree of optic atrophy may be greater in some instances than in others.
- (2) Optic atrophy and homonymous hemianopsia (6-16 per cent).
- (3) Bitemporal hemianopsia and normal optic nerves.
- (4) Optic atrophy and a central scotoma in prefixed chiasms.
- (5) Choked disk with bitemporal hemianopsia, rarely.
- (6) Choked disk with normal visual fields, very rarely.
- (7) Normal optic nerves and fields, rarely. This occurs at times even in the presence of quite large tumors.

3. DEFORMITY OF THE SELLA TURCICA.—The growth of the tumor within the sella turcica inevitably produces a change in its bony contour, the result being a characteristic ballooning out of the sella (Fig. 223). The floor becomes depressed and the underlying sphenoid sinus encroached upon. Upward expansion of the tumor produces erosion of the posterior clinoid processes and the dorsum sellae, and erosion and pointing of the anterior clinoids. The deformity is easily recognized when fully developed. In its early stages it may not be readily detected without supporting clinical signs.

4. ENDOCRINE DISTURBANCES.—Associated with the optic atrophy, the bitemporal hemianopsia, and the expansion of the sella turcica, are endocrine disturbances. These are of two types: (a) hypopituitary pictures associated with chromophobe adenomas, (b) acromegaly, associated with eosinophilic adenomas. In addition, there is (c) the basophilic adenoma which is always microscopic, never produces optic

in some cases before that of form. The bitemporal field cut may be encountered without visible changes in the optic disks, and in such instances may be associated either with normal or decreased visual acuity.

While bitemporal hemianopsia is found in some cases without optic atrophy, the latter does not occur without hemianopsia unless, of course, blindness is present and fields cannot be taken. Normal visual fields are found in rare instances. Rarely also an altitudinal hemianopsia is present. In those instances in which normal visual fields and normal optic nerves are found, it is quite probable that most of the

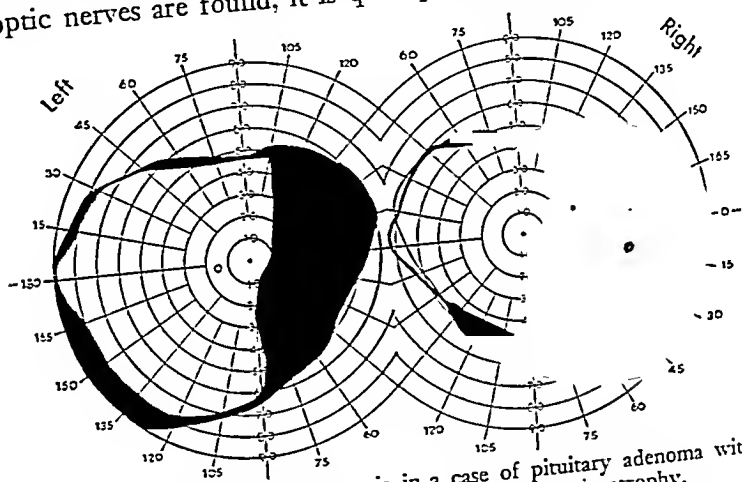


Fig. 222.—Homonymous hemianopsia in a case of pituitary adenoma with typical enlargement of the sella turcica and optic atrophy.

tumor growth has been downward into the sphenoid sinus rather than upward toward the optic nerves and chiasm. Concentrically contracted fields are sometimes found. When present they are found in association with severe damage to the optic nerves and are an indication of advanced optic atrophy.

*Homonymous hemianopsia* (Fig. 222) is found in some cases, the reported incidence varying from 6 to 16 per cent. This type of field defect is due to pressure of the tumor against one of the optic tracts owing to asymmetrical growth. Quadrantic hemianopsia is encountered in rare instances.

TABLE 2\*  
HORMONAL CHANGES ASSOCIATED WITH PITUITARY TUMORS

Type of Tumor	Pituitary Tumors				Ovarian Hormones		Testicular and Adrenal Cortical Hormones	
	Growth	Thyrotropic	Adenotrophic	Gonadotrophic	Estrogens	Pregnandiol†	Androgens	17-Ketosteroids‡
Eosinophilic	Increased	Increased		Increased early?, diminished later	Normal early, diminished later	Normal early, absent later	Normal early, diminished later	Normal or low
Basophilic	.	...	May be increased	May be increased early, diminished later	May be normal, low or high	May be present	May be normal or increased	Normal or increased
Chromophobic	.	Decreased	.....	Diminished	Diminished	Usually absent	Diminished	Diminished or absent

\* I am indebted to Dr. A. M. Rakoff for the data included in this table.

† The excretion product of progesterone, therefore usually an indicator of corpus luteum function.

‡ Based on the colorimetric determination of those steroid hormones which have a ketone group on the 17th carbon atom. In the female this test is believed to be a measure of adrenal cortical activity while in the male testicular hormones are also included.



atrophy or bitemporal hemianopsia, and is never associated with enlargement of the sella turcica.

(a) *Hypopituitary Features* (Chromophobe Adenoma).—Hypopituitarism is by far the most common of the endocrine disturbances associated with pituitary tumors. It is characterized by depression of sexual function, atrophic changes in the



Fig. 223.—Typical appearance of the sella turcica in adenoma. Balloon-shaped enlargement, pointing of the anterior clinoids, thinning of the dorsum sellae turcicae, and encroachment on the sphenoid sinus

skin and hair, adiposity, decreased metabolic rate, and high carbohydrate tolerance. The full-bloom syndrome of dystrophia adiposogenitalis (Fröhlich syndrome) is rarely seen since chromophobe adenomas are rare before puberty. Amenorrhea is common, is usually gradual in onset, is a very early symptom, and is preceded usually by irregularity and decrease in menstrual flow. Loss of libido is found in males and with it not infrequently a loss or impairment of sexual

TABLE 2\*  
HORMONAL CHANGES ASSOCIATED WITH PITUITARY TUMORS

Type of Tumor	Pituitary Tumors				Ovarian Hormones		Testicular and Adrenal Cortical Hormones	
	Growth	Thyrotropic	Adrenotropic	Comadotropic	Estrogens	Pregnanediol†	Androgens	17-Ketosteroids‡
Eosinophilic	Increased	Increased		Increased early?, diminished later	Normal early, diminished later	Normal early, absent later	Normal early, diminished later	Normal or low
Basophilic	.	..	May be increased	May be increased early, diminished later	May be normal, low or high	May be present	May be normal or increased	Normal or increased
Chromophilic	.	Decreased	. . .	Diminished	Diminished	Usually absent	Diminished	Diminished or absent

\* I am indebted to Dr. A. M. Rakoff for the data included in this table.

† The excretion product of progesterone, therefore usually an indicator of corpus luteum function.

‡ Based on the colorimetric determination of these steroid hormones which have a ketone group on the 17th carbon atom. In the female this test is believed to be a measure of adrenal cortical activity while in the male testicular hormones are also included.

atrophy or bitemporal hemianopsia, and is never associated with enlargement of the sella turcica.

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decrease in estrogens and androgens, diminution or absence of 17-ketosteroids and pregnandiol.

(b) *Acromegaly*.—The features of this are so well known as to require little description. In the fully developed case there is enlargement of the jaw, protrusion of the lower jaw, prominent eyebrows, enlargement of the hands and feet with

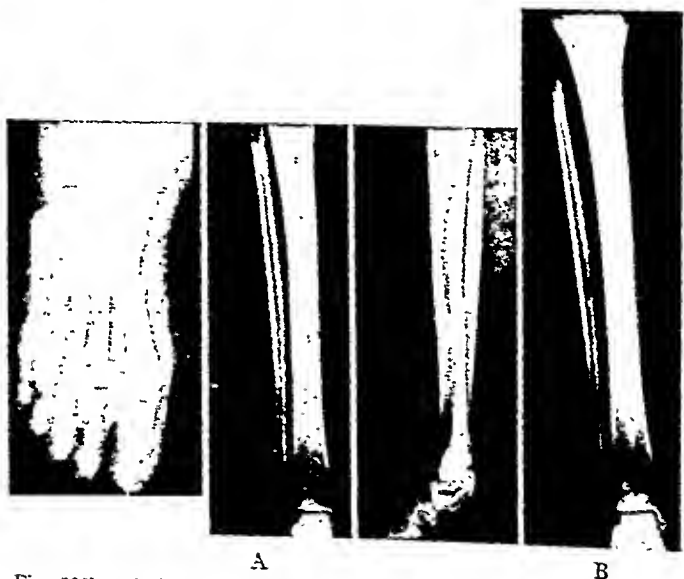


Fig. 223b.—A. Pituitary basophilism. Rather large defects can be seen in the first, third and fourth metatarsal bones and in the first terminal phalanx. This film was made shortly after admission and before x-ray treatment. The sharply circumscribed defects in the tibia can be seen throughout the shaft of the bone. Roentgenograms made before treatment. B. Roentgenogram made nine months after a series of x-ray treatments to the pituitary gland. The demineralized areas in the tibia are so completely filled in by new bone that their original sites are difficult to determine. (Courtesy of Wohl, M. G., Moore, J. R. and Young, B. R.: *Radiology*, vol. 24.)

blunt fingers and spadelike hands, thickening of the skin with wrinkling of the skin of the forehead and scalp, enlargement of the nose and lips, and enlargement of the frontal sinuses.

In early cases the changes described are found in lesser degree.

Hormonal studies reveal an increase in the production of

potence. The skin is fine, smooth and delicate. The hair becomes soft and dry and the facial hair scanty, making shaving necessary much less frequently than normal. The pubic hair becomes scanty and in males assumes a feminine distribution.



Fig. 223a.—Pituitary basophilism in a girl twenty-three years of age. *Chief complaints:* Rapid gain in weight; scant and irregular menstruation, and pains in both lower extremities. *Positive signs:* Obesity affecting face and upper trunk; growth of hair on upper lip and chin; prominent purplish striae on lower half of abdomen; basal metabolic rate minus 26 per cent; high carbohydrate tolerance. Demineralization of right tibia and metatarsal bones and phalanges. (Courtesy of Wohl, M. G., Moore, J. R. and Young, B. R.: *Radiology*, vol. 24.)

Adiposity may be present, but is often not striking in adults. It is more frequent in younger patients. The basal metabolic rate is usually low. Hormonal studies\* show a probable decrease in thyrotropic and gonadotropic hormones, a probable

\* I am indebted to Dr. A. M. Rakoff for the data concerning the hormonal studies in pituitary tumors.

anopsia, and roentgen examination of the skull for enlargement of the sella turcica. In a typical case, optic atrophy, bitemporal hemianopsia, and a characteristic enlargement of the sella turcica will be found. The diagnosis in such a case is usually not difficult.

The important problem is that of *early* diagnosis in order to save vision before it becomes too greatly involved. The difficulty lies in those cases which complain of failing or misty vision in which there is no difficulty in visual acuity or in which no evidence of optic atrophy is seen by ophthalmoscopic study. Such cases are apt to be dismissed as instances of refractive error, especially if they are relieved temporarily by glasses. A complete history in such a case will ordinarily give some clue concerning a possible pituitary tumor—menstrual difficulties, headache, asthenia, loss of libido. It is a wise principle to follow, that if there is a suspicion that a tumor may be present, visual field and roentgen studies of the skull should be done, the reason being to detect tumor early before too much pressure is made on the optic nerves and chiasm resulting in irreparable damage to vision.

Disturbance of vision is of course a common complaint and pituitary tumor is one of its less common causes, taking all causes of visual disturbances into consideration. It is partly for this reason as well as for the facts mentioned previously that many early cases of pituitary tumor are not detected. The problem can be seen conversely in the large proportion of cases with irreparable optic atrophy at the time of their first examination. Not only are many cases not detected early but too many are diagnosed too late.

Not all patients present themselves with a complaint of failing vision. Headache may be the presenting complaint, as well as menstrual disturbances. In cases with this onset pituitary tumor must be suspected if the history is of long-standing and if there are visual complaints as well.

Many cases of early pituitary tumor are assumed to be due to sinus disease, and the patient is dismissed with that diagnosis. It is essential to realize that sinus disease rarely causes optic atrophy or, for that matter, severe visual disturbances,

the growth hormone and a decreased production of the sex hormone.

Not all cases of acromegaly are associated with an eosinophilic adenoma. Some are due to hyperplasia of the eosinophilic cells without enlargement of the gland and with no signs of tumor.

(c) *Basophilism* (Cushing's Syndrome).—This endocrine picture is associated with a microscopic basophile adenoma in the majority of cases and is never found with enlargement of the sella turcica or compression of the optic nerves or chiasm. In rare instances no adenoma is found. The same picture may be produced by adrenal cortical tumors. The syndrome is characterized by obesity of the face, neck and trunk, hirsutism, osteoporosis, purple striae of the trunk and thighs and decreased sexual activity (Figs. 223a and 223b).

5. MISCELLANEOUS SYMPTOMS.—At times ocular palsies may be observed with pituitary adenomas. Of these, oculomotor paralysis of one side is most frequent and is characterized by external strabismus, ptosis, limitation of movement of the eyeball, and immobility of the pupil to light stimulation. At times abducens paralysis occurs, evidenced by internal strabismus. Ocular palsies are usually the result of extension of the adenoma beyond the sella, but they may occur without such extension.

When a pituitary adenoma breaks through its capsule and escapes into the cranial cavity, it develops the feature of an intracranial tumor. Other cranial nerve paralyses besides oculomotor, uncinatate fits, and motor paralysis may result. Diabetes insipidus is sometimes found.

#### DIAGNOSIS

The crucial problem in both the diagnosis and treatment of pituitary tumors is that of *vision*. The complaint of blurring or failing vision of gradual onset should arouse the suspicion of a pituitary tumor especially if there is a history of long standing headache, chronic menstrual disturbances, or loss of libido in a young adult or in an older person. Such a suspicion should lead to an ophthalmoscopic examination for the presence of optic atrophy, visual field studies for hemi-

and irradiation—and each has its advocates. The proponents of irradiation point to the absence of fatality by this method, while the advocates of surgery point out that the mortality is less than 5 per cent. The use of irradiation may result in valuable time lost in the preservation of vision, according to its opponents, while its advocates indicate that remission of symptoms and signs can be obtained in 50 per cent of chromophobe adenomas. The chromophile adenomas are more susceptible to roentgen therapy than the chromophobe type.

It is difficult to establish set rules concerning the use of surgery or irradiation in the treatment of pituitary adenomas. In cases with definite optic atrophy and clear evidences of pressure on the optic nerves and chiasm, operation is preferable in order to relieve the compression already existent and to prevent further compression and hence greater visual loss.

*Indications for Roentgen Therapy.*—Roentgen therapy is best reserved for the following types of cases:

1. *Early cases:*

(a) Cases with no optic atrophy, but with hemianopsia, with little or no loss of visual acuity.

(b) Cases with early optic atrophy with hemianopsia, but with normal, or near normal, visual acuity.

2. *Postoperative treatment.*

3. *Cases in which operation is refused.*

When irradiation is used, it should be followed carefully for its effect on the optic nerve, visual fields, and visual acuity. Any indication of advance in any of these factors should mean substitution of operation for roentgen therapy in order to preserve vision. Frequent ophthalmoscopic and visual field studies are necessary in order to prevent visual loss.

It may be objected that the early cases suggested for irradiation are precisely the ones best suited for operation since pressure effects are least. Since roentgen treatment is efficacious in many cases, a trial of such treatment in early cases appears advisable, especially if they can be studied adequately to prevent irreparable visual loss. That these studies are essential is clear from the fact that it is not possible to predict from the clinical studies whether vision is still recoverable and when it will become permanent.



and to recall that sinus disease and pituitary tumor may exist simultaneously in the same patient. The too ready acceptance of sinus disease as the cause of visual disturbances therefore fails to recognize these two essential points.

In view of the great importance of the early detection of pituitary tumors, there is little excuse for not erring on the safe side in suspicious cases and of making the requisite studies to establish the diagnosis—roentgen examination of the skull and ophthalmoscopic and visual field studies.

### Differential Diagnosis

The differential diagnosis of pituitary tumors is not difficult. There are few conditions which simulate the complete syndrome. There are many conditions which produce optic atrophy but few which cause optic atrophy and bitemporal hemianopsia. Lesions in the *suprasellar region* above the sella turcica produce optic atrophy and bitemporal hemianopsia. These include aneurysm, meningiomas, adenomas, hypophyseal stalk tumors and arachnoiditis. None of these conditions are associated with the typical sellar deformity of the pituitary tumor. The hypophyseal stalk tumor may be associated with sellar destruction which may rarely simulate an intrasellar tumor. Suprasellar tumors are usually associated with minor deformities such as erosion of the posterior clinoids and dorsum sellae. Endocrine disturbances are not prominent in suprasellar lesions save in the case of hypophyseal stalk tumors which are often associated with infantilism, since most of these tumors develop in children or adolescents.

Tumors or aneurysms in the *parasellar region* may produce optic atrophy but are always associated with homonymous hemianopsia, often with ocular palsies, and unilateral erosion of the sella turcica.

### TREATMENT

The treatment of pituitary adenomas is concerned largely with (1) the preservation of remaining vision, (2) the prevention of failure of vision in cases with adequate or normal sight. Two types of treatment are available—operation

and irradiation—and each has its advocates. The proponents of irradiation point to the absence of fatality by this method, while the advocates of surgery point out that the mortality is less than 5 per cent. The use of irradiation may result in valuable time lost in the preservation of vision, according to its opponents, while its advocates indicate that remission of symptoms and signs can be obtained in 50 per cent of chromophobe adenomas. The chromophile adenomas are more susceptible to roentgen therapy than the chromophobe type.

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*Indications for Surgery.*—Most cases of pituitary adenoma require operation since the indications of pressure and visual loss are usually well advanced by the time patients appear for treatment. Studies of postoperative cases show that for the chromophobe adenomas there is great variability in the rate of growth. If a recurrence is to develop, signs of it will be manifest within five years after operation in 95 per cent of cases. With operation followed by irradiation there may be remission of symptoms for 10 to 20 years. In acidophilic adenomas associated with acromegaly, operation brings good relief of the visual disturbances, but none for the endocrine disorders.

Cystic adenomas of the pituitary are not susceptible to irradiation. Operation gives best relief, but there is no way of determining beforehand whether a tumor is solid or cystic.

The duration of the visual symptoms determines the outlook in general. Cases with a shorter duration than those of visual symptoms show a greater tendency to recovery than those of longer duration, though it is well known that sudden impairment of vision may be associated with relatively little improvement after operation. The visual fields tend to parallel the improvement in visual acuity. These too are more prone to improve the shorter their duration.

## INDICATIONS FOR SURGICAL TREATMENT OF PITUITARY TUMORS

ROBERT A. GROFF, M.D., F.A.C.S.\*

THE successful treatment of all malignant tumors depends upon early diagnosis. The basis for this statement is obtained from surgical experiences where the small size, the location and the fact that the tumor has not spread to distant parts have all contributed to the ease with which complete surgical removal is effected and morbidity kept down to a minimum. This is particularly true in brain tumors where the conservative removal of tissue is so important. For example, a small tumor in the frontal lobe can be removed easily, in most instances completely, without subsequent morbidity. Whereas, if that tumor has spread to the adjoining parietal or temporal lobes, its removal cannot be effected without danger of life or of a definite permanent defect.

Pituitary tumors, although they are not classified as true brain tumors, must be considered malignant because they can not, in most instances, be removed completely and because they press upon vital structures when they become large. Early diagnosis of the presence of these tumors prevents harmful pressure upon vital structures. Likewise, it paves the way to restoration of the normal function of the pituitary gland.

An example of the effects of late diagnosis in patients with pituitary cysts is obtained from a paper by Sir Victor Horsley. He stated that by the time the patient reaches the neurosurgeon, the tumors are so large that it is practically impos-

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in over 25 per cent of these adenomas and directs the form of treatment to be used, as will be shown later.

*Symptoms and Signs.*—These pituitary tumors produce their symptoms and signs by causing a disturbance of the functional activity of the gland, and pressure upon the structures above and to the sides of the pituitary fossa or sella turcica. The former symptoms and signs are referred to as *glandular* and the latter as *neighborhood*.

The *glandular* manifestations are characteristic but they may be misinterpreted. The first complaint, of both men and women, is usually loss of libido or loss of sexual desire. In the female, the menstrual cycle is markedly retarded or stops completely. In both sexes the hair becomes scanty, fine and dry, but is particularly evident in the male, since the necessity for shaving is much reduced. The weight of the patient increases in most instances to the point of obesity. With this increase of weight there is a lowering of the basal metabolic rate in many of the patients. During examination a curious mental sluggishness will be noted and some of the patients will comment about their lack of initiative.

The *neighborhood* symptoms and signs begin with *headache*. This complaint is usually referred to the temporal regions, but the type of headache has no uniformity and no characteristic features. The cause is attributed to pressure upon the diaphragm of the pituitary fossa.

After the tumor has pushed its way above the sella turcica, it exerts pressure upon the optic nerves and optic chiasm. The patient warns the physician of this fact by complaining of *loss of vision*.

In about half of the patients, the visual loss follows a definite pattern. The adenoma compresses the inner half of both optic nerves and/or optic chiasm. The optic chiasm consists of the crossing fibers from the inner or medial half of both optic nerves. Pressure on either of these two structures, the optic chiasm or medial half of both optic nerves, will cause blindness of the nasal half of both retinae. If this visual defect is plotted on paper placed in front of the patient, it will be seen that the outer halves of both visual projections, or fields, are blind. Since the outer half of each visual field is on the

sible to remove them. His surgical experiences clearly emphasize this fact. Since the publication of his paper, the proficiency of diagnosing these tumors in their early stage has improved greatly but there remains the possibility for further improvement.

Just as the ability to recognize pituitary tumors early has improved, so has treatment advanced. Surgical technic has improved so that the tumor can be approached and dealt with more easily. In addition to this, x-ray therapy has been found to be most valuable in checking its growth. As a result of these advances, the future of patients with pituitary tumors is much brighter.

The purpose of this clinic is to give the essential features which will assist in the early recognition of pituitary tumors and to outline the present methods of therapeutic management of patients with pituitary tumor.

#### TYPES OF TUMORS

There are four types of tumors which grow most commonly in connection with the pituitary gland, as follows:

1. Chromophobe adenoma
2. Chromophile adenoma (eosinophilic adenoma)
3. Basophilic adenoma
4. Hypophyseal stalk tumor (Rathke's pouch tumor)

In addition to this group of tumors, there is a lesion called adamantinoma. This growth is rare, malignant, and need not concern us here.

Since, with the exception of the basophilic adenoma, all of these tumors are, or eventually become, surgical lesions, each will be considered separately from the clinical and therapeutic standpoints.

#### CLINICAL DATA

##### Chromophobe Adenoma

This tumor, as its name implies, is a more or less circumscribed proliferation of the chromophobe cells of the anterior lobe of the pituitary gland. Most chromophobe adenomas are solid; however, they may undergo cystic degeneration, the cyst occupying most of the tumor. This process takes place

in over 25 per cent of these adenomas and directs the form of treatment to be used, as will be shown later.

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temporal side, the defect is called *bitemporal hemianopsia*. The patient sometimes gives the history that vision is beginning to fail from the outer side of both eyes.

Other types of visual defects which may occur are blindness in the same half of each eye, known as *homonymous hemianopsia*, and blindness in one eye with general constriction in the other eye. Obviously these are late signs and the diagnosis should be made when only slight visual defects are noted.

Pressure upon the optic nerves can be confirmed by an examination of the optic disks with an ophthalmoscope. The optic disks lose their normal pink color and become pale when subjected to pressure. Depending upon the length of time pressure has been exerted upon the optic nerves and chiasm, the pallor of the disks varies up to the point of a china white color which is indicative of complete atrophy. Because this pressure is made directly on the optic structures, the outline of the optic disk is sharply defined, only the nerve head participating in the atrophy. The term *primary optic atrophy* is given to this picture. This type of atrophy is in contrast to that caused by increased intracranial pressure, in which instance the optic nerve is literally pushed into the chamber of the eye, carrying with it the retina. Actually, this process is caused by edema. The retina around the optic disk consequently takes part in the atrophy. The margins of the disk are, therefore, irregular. Atrophy thus produced is called *secondary optic atrophy*.

Occasionally the *optic disk*, because of pressure from a pituitary tumor, takes on a greenish waxy appearance in addition to the pallor. This color is pathognomonic of pituitary tumor. Optic disk pallor and the characteristic color of the disk are late signs and it must be remembered that it is not necessary to have either one to make the diagnosis.

The final link in the diagnosis of chromophobe adenoma is *enlargement of the pituitary fossa or sella turcica*. Presence of enlargement is determined by means of a lateral x-ray picture of the skull, or, better still, a picture of the pituitary fossa. The fossa will be seen to have a characteristic balloon-shaped distention.

*Comment and Summary.*—As the clinical picture of chromophobe adenoma is unfolded, it becomes apparent that the syndrome is not particularly significant until the patient developed visual disturbances. This is particularly true if the patient is a woman approaching the time of menopause. All the symptoms and signs can be mistaken for this normal physical change up to the point of beginning visual impairment. It is for this reason that pituitary tumors in patients in this age group are likely to be overlooked until marked visual disturbances are in effect.

The characteristic features of the chromophobe adenoma are:

*Subjective:*

1. Loss of libido
2. Cessation of menstruation in the female
3. Scanty hair
4. Obesity
5. Visual loss

*Objective:*

1. Bitemporal hemianopsia
2. Primary optic atrophy
3. Balloon-shaped enlargement of the pituitary fossa

### Chromophile Adenoma; Eosinophilic Adenoma

This tumor, as in the case of the chromophobe adenoma, is a cellular growth and the histological studies reveal that the eosinophilic cells of the anterior lobe of the pituitary gland have undergone proliferation. Cystic degeneration of the adenoma may occur but is not seen as frequently as in the chromophobe adenoma. Symptoms and signs are produced by the cellular growth causing a perversion in glandular secretion and by pressure of the growth upon the structures in the immediate vicinity above the pituitary fossa.

*Symptoms and Signs.*—The glandular symptoms and signs in the chromophile adenoma are distinctive. If the lesion begins to grow before the patient has reached the age of puberty, *gigantism* results. If the growth develops after the age of puberty, the syndrome is called *acromegaly*. This syndrome is characterized by a generalized increase in size of all bony structures. The face is characteristic. The jaw becomes

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lar picture which is slow in developing and not considered in many instances by the patient as abnormal. Medical advice is not sought until the neighborhood signs of visual disturbances have set in. It might be said at this time that there are tumors which present both a mixed histological and clinical picture of these two pure forms.

The following is a resume of the principal symptoms and signs of the chromophile adenoma:

Subjective:

1. Gigantism before puberty
2. Acromegaly after puberty
3. Headache, lassitude
4. Loss of libido
5. Cessation of menses in the female
6. Visual loss

Objective:

1. Signs of gigantism or acromegaly
2. Bitemporal hemianopsia
3. Primary optic atrophy
4. Balloon-shaped enlargement of pituitary fossa shown by x-ray

### Basophilic Adenoma

The diagnosis of this tumor is made on purely clinical evidence and by histological study of the pituitary gland. The tumors reported are comparatively small and one was reported the size of a "pin-head." The usual histological picture is a localized, or, at times, several localized collections of blue-staining cells, thus the term basophilic. The growth, consequently, is not a surgical problem.

*Symptoms and Signs.*—The only thing which concerns us here is the glandular signs, since neighborhood phenomena never enter the picture.

The classic syndrome when well advanced is easy to recognize. The patient is mentally dull. The face is round. In the female there is an unusual growth of hair particularly about the mouth. *Obesity* is a prominent feature and is almost entirely confined to the trunk. Over the lateral walls of the abdomen, there are striae which usually have a purplish red discoloration. The skin elsewhere may show a purplish mottling. The blood pressure is elevated. The blood calcium may be reduced and x-ray pictures of the bones, particularly of

unusually prominent and this is known as prognathism. The frontal sinuses enlarge greatly and the supra-orbital ridges attain undue prominence. The nose increases in size, sometimes becoming bulbous. The whole face is coarse featured. The tongue thickens. The hands and feet enlarge out of proportion to their normal relationship with the extremities. The skin presents a curious puffiness and the hair is coarse.

The *neighborhood* symptoms and signs are in general similar to those described for the chromophobe adenoma. The patients usually complain of *headache*. Again this symptom is caused by the tumor pressing upon the diaphragm of the sella turcica. In patients of both sexes there is loss of sexual desire or libido. In the female the menses become irregular and the flow is reduced or may stop altogether. The general reactions of the patients are sluggish, making for mental dullness. Generalized weakness is often a prominent complaint.

The symptom of *failing vision* is likewise a feature in this tumor. The cause is similar to that previously given, that is, pressure of the growth upon the optic nerves and chiasm. Similarly, in most of the patients the visual fields will show a bitemporal hemianopsia. Effects of pressure upon the optic nerve are manifested by a primary optic atrophy seen on eye ground examination. Depending upon the length of time pressure has been present, the degree of atrophy will vary.

The pituitary fossa enlarges in a fashion similar to that described for chromophobe adenoma. The fossa becomes balloon-shaped and is better seen in a special x-ray of the pituitary fossa than in a lateral view of the skull.

*Comment and Summary.*—Contrasting the patient who develops a chromophile adenoma with one that develops a chromophobe adenoma, we find that in the former the glandular signs are that of hyperpituitary function, gigantism or acromegaly. Because the skeletal changes are recognized early as abnormal, the patient seeks medical advice before the neighborhood signs of headache, visual loss and primary optic atrophy appear. The diagnosis, however, is not dependent upon these latter signs. The patient with the chromophobe adenoma, on the other hand, presents a hypopituitary glandu-

The first indication may be *visual loss*. Visual field defects may take on almost any pattern. The eyegrounds present a primary type optic atrophy, but may show choking of the disks indicative of increased intracranial pressure. In many of the patients there is definite mental retardation and a definite history of fluctuation of symptoms and signs.

One of the most valuable aids in diagnosis is an x-ray picture of the sella turcica. In the early cases the clinoid processes, either anterior or posterior or both depending upon the position of the tumor, will show erosion. In the late cases the pituitary fossa presents a saucer-shaped appearance.

From this description one gets the impression of an indefinite syndrome. This is about the most definite part of the picture except for the possibility of pituitary disease in childhood.

#### THERAPEUTIC DATA

The management of a patient in whom the diagnosis of pituitary tumor has been made depends upon the degree to which neighborhood signs of the clinical syndrome are present. *Preservation of vision* is the keynote of therapy in all pituitary lesions. The degree of visual loss and the extent of the visual field defects, therefore, are the most important features in the clinical syndrome. The glandular side of the picture is purely secondary and will improve or remain stationary if vision is attended to first.

The next important consideration in treatment is to determine whether the patient should be treated by *x-ray* or *immediate surgery*. Formerly it was thought that all tumors of the pituitary gland should be operated upon. The criteria for operation were any decrease in visual acuity and a contraction in the visual fields. At times intractable headache with other stigmata of pituitary disease and an enlargement of the pituitary fossa were considered enough evidence for surgery. In some instances the operation was followed by a course of x-ray therapy after the wound had healed, or at a future time when signs and symptoms of recurrence were beginning. This form of therapeutic management proved successful and there are patients who have survived as long as ten to fifteen years under this regimen. The objection to surgery is that it

the spine, may show demineralization. The patient becomes unusually susceptible to infection.

These signs represent those upon which the diagnosis can be made. It is suggested that since this picture is so closely allied to that of adrenal tumor syndrome studies should first be carried out to eliminate this possibility.

### Hypophyseal Stalk Tumor

This tumor arises from a vestige of the anterior lobe of the pituitary gland during its embryological development. In the embryo the anterior lobe of the gland is formed by an inward pouching of the posterior wall of the nasopharynx. This invagination closes off from the nasopharynx forming a round sac with a line of cells attaching it to the wall. As the sac rotates into position and forms the anterior lobe, it carries with it the cells which formerly connected it to the pharynx. Under ordinary circumstances these cells die but sometimes they live and are stimulated into a cystic growth. When this happens a hypophyseal stalk tumor is formed.

The cells rests for these tumors are usually just within the pituitary fossa or just above the diaphragm of the sella turcica. The tumor as it grows always occupies a position above the sella turcica and may extend primarily forward or backward. The growth itself is almost completely cystic, containing a greenish motor-oil-appearing fluid in most instances. This fluid contains cholesterol crystals. The walls of the cyst may have in it deposits of calcium and these deposits are visualized by x-ray in about 40 to 60 per cent of cases.

*Symptoms and Signs.*—This cystic tumor causes its clinical picture by pressure on the pituitary gland and upon the structures above and about the pituitary fossa. Since they develop in childhood and are rare in adult life, the diagnosis in many instances can be made. Otherwise, it is almost impossible to differentiate it from other types of parasellar lesions.

The *glandular* symptoms and signs may simulate those of hypopituitary function or may be inconspicuous. Occasionally the growth of the child is stopped at the period when the tumor starts to grow (atelioidosis).

The *neighborhood* symptoms and signs vary considerably.

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has been rapid, surgery should take preference over x-ray therapy. A rapidly progressing lesion may mean that a hemorrhage has occurred in the lesion. X-ray therapy in this case would have no effect. Visual acuity of 20/80 to 20/200, visual fields with marked defects and marked primary optic atrophy do not allow sufficient time for the use of x-ray therapy. The delay necessary to determine whether or not x-ray therapy would be beneficial might mean the difference between blindness and useful vision.

*Method of X-ray Therapy.*—The use of x-ray therapy in the treatment of patients with a chromophobe or chromophile adenoma demands close cooperation of the patient and *weekly visual field and visual acuity examinations by the ophthalmologist*. It is essential that the radiologist giving the treatment have had previous experience in the administration of therapy in these lesions or be guided by some one who has. This will obviate the possibility of incorrect dosages which might, if the doses are large, make the patient worse or, if the doses are small, fail to obtain a beneficial response. Since x-ray therapy involves the loss of hair, an experienced radiologist will minimize this sacrifice upon the part of the patient.

The first three x-ray treatments are a therapeutic test. Visual fields taken one week after the first treatment will show a slight increase in the visual field defect. This is caused by an edematous swelling of the gland. Visual fields taken one week after the second treatment will show a clear-cut improvement in the visual field defect, and the visual field taken one week after the third treatment will show further improvement. The treatment under these circumstances is producing the desired effect and should be continued until a full course has been given.

If the visual field, taken one week after the second treatment has been given, shows no improvement one additional treatment may be given. Should the visual field after this treatment fail to show any response, the treatment should be stopped and surgery be performed as soon as possible. Following this plan will limit surgery to only those patients who require it and will accomplish the keynote of therapy—preservation of vision.

entails a mortality risk of from 5 to 10 per cent, and that in some instances, if the visual acuity is particularly low, the vision in that eye might be blotted out regardless of the care taken to prevent trauma to the optic nerves during the operation.

Within the past six or more years it has been found that x-ray therapy is effective in diminishing the size of the solid pituitary tumors. This therapy has no effect on those tumors which have undergone cystic degeneration or upon the hypophyseal stalk tumor before it has been operated upon. These facts have led us to change the therapeutic management of pituitary tumors.

### Chromophobe and Chromophile Adenomas

The plan of therapeutic management in patients with either one or the other of these lesions is to use x-ray therapy whenever possible as the only form of therapy. This general rule involves careful consideration.

When the diagnosis is made early no hesitancy in the use of x-ray need be entertained. By early diagnosis is meant that the visual loss and the visual field defects are not marked. This can best be explained by an example. Given a woman who has become obese during the past year, has lost her sexual desire and her menstrual period has stopped. During the past three months she has complained of headache and for the past month or so has noticed a decrease in vision. On examination she is found to have all the stigmata of hypopituitary function. The visual acuity is 20/40 in both eyes and the visual fields show a slight bitemporal loss of vision. The optic disks are questionably atrophic. The important signs in this patient are the moderate visual disturbances and the historical data pointing to a steady progress of the disease. If the historical data had suggested fluctuation in the symptoms and signs, the possibility of cystic tumor would have to be considered and the value of x-ray therapy questioned. However, as the data stand, the patient would be a good candidate for the use of x-ray therapy.

When visual disturbances are marked, or there is any suggestion in the historical data that the progress of the disease

has been rapid, surgery should take preference over x-ray therapy. A rapidly progressing lesion may mean that a hemorrhage has occurred in the lesion. X-ray therapy in this case would have no effect. Visual acuity of 20/80 to 20/200, visual fields with marked defects and marked primary optic atrophy do not allow sufficient time for the use of x-ray therapy. The delay necessary to determine whether or not x-ray therapy would be beneficial might mean the difference between blindness and useful vision.

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If the visual field, taken one week after the second treatment has been given, shows no improvement one additional treatment may be given. Should the visual field after this treatment fail to show any response, the treatment should be stopped and surgery be performed as soon as possible. Following this plan will limit surgery to only those patients who require it and will accomplish the keynote of therapy—preservation of vision.

### Basophilic Adenoma

This tumor, as previously stated, is microscopic in size and therefore does not come under the consideration of the surgeon. X-ray therapy has proven most effectual in controlling this tumor. Since visual symptoms and signs are absent in the patient, the criterion for improvement is based on the clinical course. The radiologist and clinician decide upon the amount and number of courses of therapy.

### Hypophyseal Stalk Tumors

These cystic tumors do not respond to x-ray therapy if given before operation. Since the signs and symptoms are produced by pressure upon vital structures, operation should be performed as soon as the diagnosis is made. When the diagnosis is doubtful, a therapeutic test may be given with the same precautions outlined above under x-ray therapy in the chromophobe and chromophile adenomas.

The postoperative management of the patients should include a complete course of x-ray therapy from two to four weeks after the operation. In 1934, Frazier and his collaborators showed conclusively that postoperative x-ray therapy to hypophyseal stalk tumors stopped or checked the secreting cyst wall, which was not removed, for as long as two and one-half years. Without x-ray therapy, the cyst wall reformed and filled up with fluid in about six months. These observations have materially lengthened the lives of patients with these tumors.

### COMMENT AND SUMMARY

Pituitary tumors are no longer considered a surgery "must." With the knowledge that x-ray therapy will control the growth of solid tumors until they become radioresistant early diagnosis has reduced the incidence for the necessity of surgery. The criteria for the use of x-ray therapy are based entirely upon the amount of visual disturbance and whether or not that visual disturbance responds to x-ray therapy. Cystic tumors, including the hypophyseal stalk tumor, do not respond to x-ray therapy, so that in these lesions immediate surgery is indicated as soon as the diagnosis is made. When

administering x-ray therapy, it is essential that the suggestions outlined above be followed closely. All pituitary tumor patients should have a check made on their visual fields every three to six months after a course of x-ray therapy or an operation.



## THE DIAGNOSIS AND TREATMENT OF THYROID DISEASE

EDWARD ROSE, M.D., F.A.C.P.\*

### HYPOTHYROIDISM

#### Diagnosis

THE recognition of hypothyroidism is a most satisfactory experience because the therapeutic rewards are among the richest in medicine. The picture of typical myxedema is so well known that it need only be outlined here. The commonest complaints include fatigue, sensitivity to cold, mental and physical sluggishness, loss of memory, dryness and scaliness of the skin, loss of hair from the scalp and eyebrows, vague aches and pains in the back and extremities, constipation and flatulence, sterility and loss of libido, impotence in the male, and various types of menstrual disorders. The patient is slow and tortoise-like in his movements and mental reactions, with a dry, parchment-like skin which is frequently yellowish. There may be a butterfly patch of erythema across the cheeks and the bridge of the nose. The face and hands present a puffy appearance, especially marked about the eyes. The simulation of obesity, however, is usually deceptive, for these patients are generally not overweight and are in fact often malnourished beneath their superficial padding of coarse skin and the subcutaneous layer of myxoid infiltration. The hair of the scalp and eyebrows is dry and sparse. The tongue is often thick, the heart rate slow, and the abdomen often abnormally distended. The voice is usually hoarse or croaking. This picture is so striking that it seldom escapes recognition.

Hypothyroidism may produce a variety of clinical pictures quite different from that of classical myxedema. The physician must be on the alert to penetrate these atypical guises,

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since the response of atypical forms of thyroid deficiency to proper treatment is just as gratifying as that of myxedema.

Many patients with hypothyroidism complaining of vague pains, aches, and stiffness in the back or extremities are frequently treated ineffectively under mistaken diagnoses of arthritis, myositis, neuritis and spondylitis. In other instances the presenting complaint may be indigestion, flatulence, constipation, anorexia or insomnia. Severe hypochromic anemia or true primary anemia may complicate the hypothyroid state, particularly when there is achlorhydria and the diet has been deficient in anti-anemic factors. (Jaffe<sup>2</sup> has described a curious aplastic type of anemia, quite resistant to treatment, associated with marked atrophy of the thyroid acini and fibrosis of the gland.) Various vitamin deficiencies, including pellagra, may follow the anorexia. A variety of gynecological complaints without other symptoms of thyroid deficiency may include menorrhagia, metrorrhagia, amenorrhea, dysmenorrhea, sterility and frigidity. Urinary retention and ascites, as well as pericardial effusion, may dominate the clinical picture. Myxoid infiltration of the myocardium and coronary artery degeneration which are common in hypothyroidism may proceed unrecognized to a point where anginal or congestive circulatory symptoms first lead the patient to the clinic. Nervous and psychic phenomena occasionally constitute the chief presenting symptoms; these may include various types of schizoid or anxiety states, depressions, dementias, mania, myotonia, delirium, coma or convulsions. It is possible that some of these neurological phenomena are associated with the vascular sclerosis common in hypothyroidism. Many patients complain only of physical and mental fatigue and present no important physical findings; most of them give histories of prolonged and ineffective treatment under such diagnoses as hypotension, neurasthenia, anemia and vitamin deficiencies.

We have also observed some patients presenting a picture which we have called "paradoxical" hypothyroidism. These patients are usually underweight and complain chiefly of nervousness, fatigability, insomnia and palpitation. Both systolic and diastolic blood pressures are usually somewhat low.

There is often a mild or moderate tachycardia, tremor, and sometimes slight thyroid enlargement. Despite the resemblance to hyperthyroidism, the low basal metabolic rate, hypercholesteremia and response to thyroid therapy leave no doubt as to the diagnosis.

The two most important objective aids in the diagnosis of hypothyroidism in the adult are, first, *decrease in the basal metabolic rate*, and second, *increase in the cholesterol content of the serum*. To these may be added a third important finding in children; i.e., *x-ray evidence of delay in bony growth and development*.

There is some difference of opinion regarding the limits of the normal variation in the basal metabolic rate. For practical purposes it is best to consider any reading between  $-15$  and  $+15$  per cent as within normal limits. Most basal metabolism determinations are made upon ambulatory patients; in such patients it is usually wiser to consider the true basal metabolic rate as being about 5 per cent lower than the figure obtained in the laboratory. Some perfectly healthy persons have basal metabolic rates consistently between  $-15$  and  $-25$  per cent. Several abnormal conditions other than hypothyroidism are associated with decrease in the basal metabolic rate. These include (1) extreme malnutrition or cachexia from any cause, unless accompanied by fever, (2) nephrosis, (3) some patients with diabetes, (4) anorexia nervosa, (5) anterior pituitary failure (Simmonds' disease),\* (6) postinfectious states, and (7) so-called idiopathic hypometabolism. This latter group, described by Thurman and Thompson,<sup>2</sup> includes patients who are suspected of thyroid deficiency because of their appearance, typical complaints, slow heart rates, and cool dry skins. Their metabolic rates are low. Instead of improving under thyroid therapy, they may actually be made worse by it. Increased nervousness and tachycardia are usually the only results of treatment, and the basal metabolic rate fails to rise to normal.

It is now generally recognized that hyperthyroidism may be associated with basal metabolic rates consistently within the absolute limits of normal variation. We have long been interested in the converse possibility, that hypothyroidism may exist in association with a "normal" basal metabolic rate. While complete proof of this hypothesis is still lacking, certain clinical experiences have led us to suspect that occasionally this may be the case. In such cases, the usual basal metabolic rate may have been consistently above normal prior to

\* In both pituitary failure and certain stages of anorexia nervosa it is probable that the fall in basal metabolism is due in large part to secondary thyroid deficiency.

the development of thyroid deficiency. Thus there are occasionally individuals in good health, with basal metabolic rates around  $+20$  per cent. If such a person should develop hypothyroidism, a fall in his basal rate to zero would be equivalent to a decline from a normal level of zero to  $-20$  per cent.

Since the excellent paper by Hurxthal,<sup>3</sup> numerous observations have confirmed the frequency of increase in serum cholesterol content in hypothyroidism. There is still some difference of opinion regarding the upper limits of the normal concentration of serum cholesterol. This is probably due largely to variations in laboratory technic. Thus one may find the upper limits of normal stated as 180 to 300 mg. per 100 cc. of serum. In our hospital we regard 225 mg. per 100 cc. as about top normal, 225-250 mg. as questionably increased, and any figure above 250 mg. as definitely high. Normally about 60 per cent of the total serum cholesterol is free and about 40 per cent is present as cholesterol ester. The increase in hypothyroidism occurs chiefly in the free cholesterol. Total cholesterol concentrations as high as 600 mg. per 100 cc. of serum may be seen in hypothyroidism. Marked increases are more common in myxedema than in other types of hypothyroidism, but classical myxedema may occasionally be seen with normal cholesterol levels. The hypercholesteremia usually declines promptly with adequate doses of thyroid and some writers regard such changes as a more accurate index of therapeutic response than variations in the basal metabolic rate. Hypercholesteremia also occurs in lipid nephrosis, biliary obstruction, diabetes, late pregnancy, xanthomatosis, Gaucher's disease, Niemann-Pick's disease and pituitary basophilism.

Attention has recently been called by Means, Hertz and Lerman<sup>4</sup> and by Lerman and Stebbins<sup>5</sup> to a type of anterior pituitary deficiency (Simmonds' disease) in which myxedema dominates the clinical picture. In such patients the myxedema is the result of thyroid failure which is secondary to failure of the anterior lobe of the pituitary. There is concomitant failure of other endocrines dependent upon the pituitary, especially the adrenals and gonads. While such patients appear typically myxedematous at first glance, closer investigation may reveal a history of early amenorrhea, following a complication of pregnancy or labor, unusual atrophy of the breasts and loss of pubic and axillary hair, atrophy of the genitals, and a degree of hypotension not common in primary myxedema. Laboratory studies may show a marked increase in insulin sensitivity, a decrease in the urinary excretion of follicle-stimulating hormone and 17-ketosteroids, and a decreased ability to retain sodium chloride after salt restriction. Such patients may be precipitated into dangerous adrenal fail-

ure comparable to the crisis of Addison's disease if the initial thyroid therapy be too vigorous. Any patient with myxedema reacting unfavorably to early thyroid therapy should therefore be suspected of this so-called "pituitary type" of myxedema. Furthermore, in all patients presenting the picture of myxedema, careful inquiry should be made regarding the features mentioned above which might point toward a primary deficiency of the anterior pituitary.

The diagnosis of hypothyroidism *in childhood* is not always simple. The classical picture of cretinism is by no means always present. The child may be nervous or hyperkinetic instead of dull and sluggish, underweight rather than overweight. Anemia, anorexia, various types of mental abnormality, delayed or abnormal dentition, constipation, deafness, muscular incoördination, fatigability, retardation of skeletal or genital growth and abnormal behavior patterns are all symptoms which may dominate or mask the clinical picture. Hypercholesteremia is frequent but not constant. Disappearance of the normal creatinuria of childhood may be of diagnostic assistance at times. In our experience, however, the most consistent objective finding in childhood hypothyroidism is roentgen evidence of retarded bony development. Wilkins and his associates<sup>6</sup> have described variations in serum cholesterol content following standard doses of thyroxin which they consider helpful in the diagnosis of doubtful cases.

With due regard for the usefulness of all the objective methods which have been mentioned in the diagnosis of thyroid deficiency, there is one simple clinical rule upon which, after all, the diagnosis must usually stand or fall. *If the patient responds favorably to properly controlled doses of a known potent thyroid preparation given over an adequate period of time, hypothyroidism has probably been present.*

### Treatment

The results of treatment in thyroid deficiency are among the most gratifying in medical practice. The changes which occur in the typically myxedematous patient are often dramatic, and are so well known that they hardly require a detailed description. Suffice it to say that the skin once more

the development of thyroid deficiency. Thus there are occasionally individuals in good health, with basal metabolic rates around  $\pm 20$  per cent. If such a person should develop hypothyroidism, a fall in his basal rate to zero would be equivalent to a decline from a normal level of zero to  $-20$  per cent.

Since the excellent paper by Hurxthal,<sup>3</sup> numerous observations have confirmed the frequency of increase in serum cholesterol content in hypothyroidism. There is still some difference of opinion regarding the upper limits of the normal concentration of serum cholesterol. This is probably due largely to variations in laboratory technic. Thus one may find the upper limits of normal stated as 180 to 300 mg. per 100 cc. of serum. In our hospital we regard 225 mg. per 100 cc. as about top normal, 225-250 mg. as questionably increased, and any figure above 250 mg. as definitely high. Normally about 60 per cent of the total serum cholesterol is free and about 40 per cent is present as cholesterol ester. The increase in hypothyroidism occurs chiefly in the free cholesterol. Total cholesterol concentrations as high as 600 mg. per 100 cc. of serum may be seen in hypothyroidism. Marked increases are more common in myxedema than in other types of hypothyroidism, but classical myxedema may occasionally be seen with normal cholesterol levels. The hypercholesteremia usually declines promptly with adequate doses of thyroid and some writers regard such changes as a more accurate index of therapeutic response than variations in the basal metabolic rate. Hypercholesteremia also occurs in lipid nephrosis, biliary obstruction, diabetes, late pregnancy, xanthomatosis, Gaucher's disease, Niemann-Pick's disease and pituitary basophilism.

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3:2 is recommended by the manufacturers. Further clinical experience with this preparation would seem desirable before its effects can be properly evaluated.

*Thyroxin* is commercially available both for oral and parenteral administration. Its oral use rarely offers any advantage over desiccated thyroid, although one may encounter an occasional patient who seems to respond better to thyroxin. When given orally, and assuming adequate absorption, 0.3 mg. of thyroxin is approximately equivalent to 1 grain (65 mg.) of desiccated thyroid of average potency. The chief usefulness of thyroxin at present is in treating patients unable or unwilling to swallow medication, or in whom a rapid and powerful therapeutic effect is desired. In such instances, 5 to 10 mg. of crystalline thyroxin may be given intravenously in alkaline solution. The basal metabolic rate will be raised about 3.2 per cent per milligram of thyroxin, the effect appearing within forty-eight hours and reaching a maximum in six to eight days.

*Principles of Treatment.*—The treatment of hypothyroidism will be more effective if the following principles are considered:

1. There is a wide individual variation in tolerance to desiccated thyroid. *The optimal dose for each patient, therefore, must be determined by cautious experiment.* Although, in general, sensitivity to thyroid medication increases with the severity of thyroid failure, the basal metabolic rate before treatment is not always a reliable index to initial dosage. It is usually wiser to begin with a small arbitrary dose ( $\frac{1}{4}$  to  $\frac{1}{2}$  grain daily in adults,  $\frac{1}{20}$  to  $\frac{1}{10}$  grain daily in children), and then to increase gradually until that dose is attained which gives optimal therapeutic effects without symptoms of overdosage. The optimal daily dose may range from  $\frac{1}{4}$  grain to 10 grains or more; in children it may occasionally be less than  $\frac{1}{4}$  grain daily. The daily requirement may be administered in a single dose, given at any time of the day. By following the above-mentioned principles, one may avoid certain pitfalls. These include: (a) the precipitation of adrenal insufficiency in cases of pituitary myxedema; and (b) the production of anginal symptoms or even myocardial infarc-



resumes its normal texture and appearance, the myxoid infiltration disappears from the subcutaneous and submucous tissues, there is regrowth of hair on the scalp and in the eyebrows, the facial and orbicular puffiness disappears, the face resumes a normally animated expression, and the patient's mental and physical reactions regain a normal tempo. The cardiac rate increases and if hypertension be present, there is frequently some reduction in both systolic and diastolic blood pressures. Symptomatic relief is often almost complete. Objectively, the basal metabolic rate rises, the serum cholesterol content falls, and the electrocardiogram shows a return of the previously low T-waves to normal height. There is frequently an increase in urinary output, and the slight increase in serum protein which is often present in myxedema disappears. Likewise, in the patient with hypothyroidism without myxedema, thyroid therapy is usually highly successful.

The physiological effect of *desiccated thyroid substance* reaches its maximal level gradually and likewise diminishes gradually after withdrawal. While some effects become apparent within a few days, the maximal effect of a uniform daily dose of desiccated thyroid upon metabolism is usually not manifest until treatment has been continued about four weeks. When therapy is withdrawn, the basal metabolic rate usually does not return to its pretreatment level for about three weeks. Any standard brand of U.S.P. desiccated thyroid substance will prove satisfactory.

At present there is no official biological standard of potency for desiccated thyroid, although the iodine content is required to be between 0.17 and 0.23 per cent. Because of this, there is a wide variation in the calorigenic activity of various standard brands. Thus, Lerman and Salter<sup>7</sup> a few years ago found a variation of as much as 400 per cent among several tested brands. The Burroughs and Wellcome product, the dosage of which is expressed in terms of fresh gland weight, has the lowest potency, grain for grain, while the Parke, Davis product probably has the highest potency.

The Maltine Company has recently presented a thyroid preparation called "Proloid," which is said to consist chiefly of thyroglobulin derived from the acinar colloid. It is claimed that this substance possesses all the metabolism-raising effect of desiccated thyroid with minimal exciting effect upon the heart.\* An initial dosage ratio to standard brands of thyroid of

\* Some recent evidence suggests that the thyroid may contain a principle exerting a specific stimulating effect upon the heart rate, independent of the metabolism-stimulating principle.<sup>8, 9</sup>

3:2 is recommended by the manufacturers. Further clinical experience with this preparation would seem desirable before its effects can be properly evaluated.

*Thyroxin* is commercially available both for oral and parenteral administration. Its oral use rarely offers any advantage over desiccated thyroid, although one may encounter an occasional patient who seems to respond better to thyroxin. When given orally, and assuming adequate absorption, 0.5 mg. of thyroxin is approximately equivalent to 1 grain (65 mg.) of desiccated thyroid of average potency. The chief usefulness of thyroxin at present is in treating patients unable or unwilling to swallow medication, or in whom a rapid and powerful therapeutic effect is desired. In such instances, 5 to 10 mg. of crystalline thyroxin may be given intravenously in alkaline solution. The basal metabolic rate will be raised about 3.2 per cent per milligram of thyroxin, the effect appearing within forty-eight hours and reaching a maximum in six to eight days.

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tion in patients with myxedema hearts or coronary artery disease. In such patients, circulatory catastrophe may follow the suddenly increased demands upon the heart due to rapid rise in the basal metabolic rate.

2. The optimal dosage requirement of desiccated thyroid can be determined much more easily if the same commercial preparation is used throughout the entire period of treatment, thus avoiding the variations in potency of different preparations. The name of the product desired should be specified on the prescription, and the patient's record should contain a notation of the brand ordered.

3. Treatment should be aimed at the continued maximal control of symptoms rather than the arbitrary restoration to normal of objective aberrations such as the decrease in metabolic rate or the rise in serum cholesterol. Symptomatic relief may precede the return of the basal metabolic rate and the serum cholesterol to normal levels. In such cases, it is usually better to keep the dosage of thyroid at that amount which controls symptoms.

4. Patients should be kept under close supervision until their optimal dosage has been determined, and closely watched for evidence of *overdosage*. Such evidence may include nervousness, irritability, insomnia, palpitation, tachycardia, various types of cardiac arrhythmia, anginoid pain, flushing or a sensation of heat, abnormal sweating, abdominal cramps, nausea, diarrhea and headache. The full-blown picture of hyperthyroidism, including goiter and exophthalmos, has occasionally followed prolonged thyroid therapy. Rarely dermal reactions apparently due to sensitivity to thyroid substance may be seen. When evidence of overdosage appears, the daily ration of thyroid should be reduced, or if the symptoms be severe, omitted altogether for a few days or a week, and then resumed at a lower level. *The treatment of hypothyroidism should never be permanently abandoned because of the appearance of signs or symptoms of overdosage.* This is particularly important in the treatment of cretinism or childhood hypothyroidism, because in these cases prolonged interruption of therapy may lead to irreversible mental deterioration. We have encountered several tragic examples of such

mistaken interruptions of treatment. Even when the patient's tolerance has been determined, he should not be dismissed, but should be instructed to report at least every three or four months for inspection. Tolerance occasionally varies without apparent cause. During pregnancy, the mother's necessary ration may have to be increased. In treating children, one must provide not only an amount of thyroid necessary for the patient's immediate needs, but sufficient extra amounts to provide for the necessary requirements of growth.

Hypothyroidism developing after thyroidectomy is frequently only temporary, and often disappears after a few months when there has been adequate regeneration of the remaining thyroid tissue. Spontaneous hypothyroid states are usually permanent and require treatment throughout the patient's lifetime. Since thyroid function occasionally recurs spontaneously, it is advisable to withdraw therapy for about four weeks once every year or two, to determine whether or not adequate thyroid function has been regained.

Desiccated thyroid is of limited value in the treatment of nonthyrogenous obesity, and its use for this condition should be limited to that of an adjuvant agent. Most patients with so-called simple obesity have normal metabolic rates, and their total metabolism is often greater than normal. Such weight loss as may be produced by thyroid in such cases is actually due to a mild or moderate hyperthyroid state, and must therefore be regarded as the result of an abnormal and sometimes dangerous condition.

#### HYPERTHYROIDISM

##### Diagnosis

There is still no single reliable sign, symptom or test to aid in the diagnosis of hyperthyroidism. In the frequent and important problems of differential diagnosis involving this disease, we must therefore rely upon evaluation of a pattern or conjuries of phenomena. A reliable objective test has been sought without avail for many years. The most promising of such tests at the present time appear to be: (a) *determination of the blood iodine level*,<sup>10</sup> usually increased in hyperthyroidism; and (b) *impairment of galactose tolerance* following oral administration of this sugar.

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tachycardia, in our experience, has been the most constant single phenomenon. Next in order may be listed enlargement of the thyroid gland (sometimes difficult to demonstrate), weight loss, objective or subjective nervousness, emotional instability, fatigue and muscular weakness. Increased appetite and diarrhea are not nearly so common as is generally believed. Thyrotoxic patients instead of losing weight may actually gain considerably, either as a result of inordinate appetite overcompensating for weight loss or from edema due to heart failure. One of our patients, an employee in a candy store, gained 20 pounds as a result of unlimited opportunity to indulge her increased appetite for sweets.

*Atypical Forms of Hyperthyroidism.*—The important atypical forms of hyperthyroidism may be described briefly as follows:

1. A form in which the picture of nutritional deficiency is predominant. In these patients there is usually marked evidence of weight loss or even cachexia occasionally complicated by nutritional edema. Muscular weakness and wasting may be extreme. The appetite is usually poor and there is often achlorhydria and moderate hypochromic anemia. Such manifestations of vitamin deficiency as glossitis, stomatitis, extreme anorexia, flatulence, diarrhea, trophic changes in the skin, hair and nails, arthralgia, visual disturbances and peripheral neuritis may be seen. Psychotic symptoms, muttering delirium or coma may occur, and perhaps represent the "encephalopathia basedowica" described in the European literature. Many of the patients described by Lahey<sup>12</sup> as the "apathetic type," in whom obvious nervousness and marked tremor are absent, probably fall within this group. We have at times noted in these patients a curious type of speech—rapid, muttering, tremulous—which has led to the correct diagnosis. Tachycardia is usually present, but not often marked. Goiter and eye signs may be minimal or absent, and the degree of elevation of the basal metabolic rate is usually not great. These patients present grave surgical risks and preoperative therapy requires more than iodine alone. Careful attention to improvement in nutrition is of the greatest importance before operation. These cases are often mistakenly diagnosed as primary vitamin deficiency, malignancy or some type of neurological disorder. The usually persistent tachycardia, frequent slight fever and thyroid enlargement, as well as the occasional slight exophthalmos or retraction of the lids are important diagnostic clues.

2. A form in which psychic, emotional or personality changes dominate the clinical picture. These patients are frequently well nourished. They are often treated for long periods of time for various psychoses or neuroses, before recognizable evidence of hyperthyroidism appears. The basal metabolic rate is of limited diagnostic value in these cases, but again tachycardia and slight thyroid enlargement are valuable guideposts. Striking changes in personality follow successful treatment of these cases.

3. A form in which symptoms of heart disease may mask the underlying hyperthyroidism. These patients form an extremely important group

There are still practical objections to the complete acceptance of both of the above-mentioned tests. The accurate determination of blood iodine concentration requires technical skill and equipment available in only a few laboratories; likewise there still appears to be some difference of opinion regarding the normal limits of blood iodine concentration. The galactose tolerance test, as advocated by Althausen,<sup>11</sup> is admittedly abnormal in at least two other diseases, hepatic insufficiency and osteitis deformans, and its specificity in hyperthyroidism does not yet seem to have been established.

Far too much reliance is still placed upon the finding of an *increased basal metabolic rate*. The accuracy of this determination depends largely upon the tranquillity and coöperation of the subject, factors which are too frequently overlooked in the evaluation of the result. In addition, actual increases in metabolic rate are often found in the following states: (a) fever (a rise of about 7 per cent for each degree Fahrenheit of fever); (b) hypertension; (c) pregnancy, especially in the third trimester; (d) congestive heart failure; (e) certain blood dyscrasias and lymphoblastomatous diseases, such as polycythemia, leukemia, and Hodgkin's disease; (f) certain pituitary disorders such as acromegaly and sometimes Cushing's disease; (g) sometimes in diabetes; and (h) sometimes in the anemias. A few healthy persons have basal metabolic rates which remain consistently a little above the upper limit of the normal zone.

Basal metabolic rates within the "normal" zone may be found in association with hyperthyroidism. This may result from a temporary fall in the basal metabolic rate without concomitant remission of the other phenomena of the disease. In other instances, a "normal" figure actually represents a rise in the metabolic rate in a patient whose usual metabolism verged on the lower limits of the normal zone prior to the development of thyrotoxicosis. Such patients may show a fall in basal metabolism to substandard levels after treatment. The serum cholesterol is often low in hyperthyroidism, but by no means constantly so. Some diagnostic aid may at times be obtained from fluoroscopic study of the heart. In about 50 per cent of thyrotoxic patients, increased prominence or pulsation of the pulmonary artery may be seen, and the excursion of the cardiac border is often abnormally wide and forceful. In doubtful cases, the use of iodine as a diagnostic test may be justified. Definite decrease in pulse rate and basal metabolism, and subjective improvement following a week or ten days' trial with iodine may be considered strong evidence of hyperthyroidism.

Hyperthyroidism often masquerades under a variety of misleading guises. Among the typical signs of the disease,

of periodic paralysis (nonfamilial) have been reported as well as paralysis of external ocular muscles without exophthalmos.<sup>14</sup>

7. In rare instances, the abrupt onset of thyroid crisis may be mistaken for acute mania or delirium from other causes. A careful inquiry into the history is especially important in these cases.

Conversely, several unrelated disorders may be mistaken for hyperthyroidism. These may be listed as follows:

1. Functional nervous disorders, including a variety of neuroses, anxiety states, psychoses, involutions states and hysteria. These are especially confusing when accompanied by tachycardia or slight thyroid enlargement.

2. Certain organic nervous diseases, including Sydenham's chorea, the earlier stages of Parkinson's disease, multiple sclerosis, and disorders associated with lesions of the basal ganglia in older patients.

3. Cardiovascular disorders. Of these, the most important is essential hypertension, especially when accompanied by tremor, tachycardia, increase in metabolic rate, nervousness and weight loss. *The diagnosis of hyperthyroidism should be made with extreme caution in the presence of persistent diastolic hypertension (90 mm. Hg or above).* Mitral stenosis may lead to diagnostic errors because of the palpitation, tachycardia, nervousness and flushing which so often occur with it. Functional and postinfectious tachycardias and neurocirculatory asthenia are also frequent sources of infection. In this connection it may be pointed out that cold, clammy hands and feet so common among neurocirculatory asthenics are rarely seen in hyperthyroidism.

4. The syndrome of autonomic imbalance, in which the clinical picture may closely resemble that of hyperthyroidism. Absence of weight loss and thyroid enlargement, and persistently normal basal metabolism may be of diagnostic aid.

5. Uncontrolled diabetes may in rare instances present a confusing picture simulating hyperthyroidism.

6. Tachycardia, weight loss, nervousness and tremor as in hyperthyroidism have been described by Netherton<sup>15</sup> in certain cases of syphilis. The symptoms are said to disappear under antisyphilitic therapy. We have seen two such cases.

7. Chronic lymphatic leukemia.<sup>16</sup>

8. Early pulmonary tuberculosis, especially when accompanied by slight thyroid enlargement and increased metabolic rate.

## Treatment

Subtotal thyroidectomy after suitable preoperative preparation is the treatment most generally favored for hyperthyroidism at the present time. There still remains, however, some divergence of opinion regarding the relative merits of various therapeutic agents. Our own opinions are based on personal experience and do not necessarily reflect the consensus of those interested in thyroid disease. In evaluating



because the results of thyroidectomy are so brilliant and because the victims are usually doomed to invalidism and death unless the cause is found. These thyrocardiac patients fall into two general groups: (a) Those in whom frequently recurring bouts of tachycardia or arrhythmias (usually auricular fibrillation) are prominent and in whom these disturbances of rate and rhythm eventually become continuous. This state of intermittent or continuous arrhythmia may persist for several years, while the other signs and symptoms of hyperthyroidism remain minimal or undetected. Sooner or later, however, congestive heart failure usually appears if the thyroid remains untreated. (b) The second group includes those patients who are first seen after the advent of congestive heart failure. The attention of the clinician is often misdirected to a search for a nonexistent cause, i.e., congenital, rheumatic, luetic, hypertensive or sclerotic heart disease. Valuable time is frequently lost by waiting for the patient to respond to the usual treatment of congestive failure, when such response must actually await the removal of the principal offending cause—the toxic thyroid gland. Tachycardia in these patients is not always striking and its significance is sometimes masked by auricular fibrillation; likewise, actual weight loss may be concealed by edema. Palpable thyroid enlargement may be difficult to demonstrate. In some cases the goiter appears only as a small nubbin or nodule above the clavicle or suprasternal notch and is easily overlooked. Sometimes the entire gland is intrathoracic and the only clue to its presence may be tracheal deviation or symptoms of upper mediastinal pressure. Mild or moderate anginal pain is common in all forms of hyperthyroidism, but is rarely so predominant as to lead to a mistaken diagnosis of primary coronary artery disease. *In any patient with tachycardia, continuous or recurrent arrhythmia, or congestive heart failure in whom the cause is not obvious, hyperthyroidism should be suspected.* It should not be forgotten that hyperthyroidism may coexist with precedent heart disease due to other causes. It has indeed been believed in recent years that hyperthyroidism alone is incapable of producing cardiac failure, and that other preceding or coexistent causes are prerequisites. It may be said parenthetically, however, that there is considerable reason to believe that hyperthyroidism may at times be solely responsible for congestive failure.

4. Uncommonly gastro-intestinal complaints may be sufficiently prominent to cause an incorrect diagnosis of colitis, gallbladder disease, peptic ulcer, or appendicitis. The abdominal pain of hyperthyroidism is usually generalized, cramplike, intermittent and often associated with diarrhea. The complete simulation of gallbladder or peptic ulcer pain is quite rare. It is almost unpardonable to mistake the abdominal symptoms of hyperthyroidism for appendicitis, but we have seen this error in at least one case.

5. Hyperthyroidism may be associated with skeletal decalcification. This is occasionally followed by severe arthralgia, bone pain or even crush fractures of the vertebrae with severe backache. Such symptoms are commoner in middle-aged or elderly persons and may in rare instances be so marked as to overshadow the other phenomena of hyperthyroidism.

6. Clinical pictures resembling various muscular and neuromuscular dystrophies may appear in hyperthyroidism. Several cases of myasthenia gravis associated with toxic goiter have been reported,<sup>12</sup> some of them also presenting persistent enlargement of the thymus. Amyotrophic lateral sclerosis and spinal muscular atrophy may be simulated. Occasional cases

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any method of treatment, two points should be borne in mind: (1) since the ultimate cause of hyperthyroidism is obscure, all forms of treatment remain empirical; and (2) hyperthyroidism is usually a cyclic disease with frequent remissions, and spontaneous permanent recovery may occur without specific therapy.

"MEDICAL" TREATMENT.—This consists of physical and mental rest, high caloric intake, sedatives, extra vitamins, psychotherapy, removal of focal infection, and the intermittent use of iodine. This form of treatment is still recommended before recourse to surgery by some clinicians and is more widely followed in practice than is generally believed. It has little to recommend it except in certain cases of ophthalmopathy described later, and in a few mild or borderline cases in which an optimal environment is available. In most cases, the prognosis will be little different from that of the untreated disease.

IRRADIATION.—This method is at present not much employed in most large thyroid clinics except as a means of preparing bad risks for thyroidectomy or of treating post-operative recurrences. With proper technic and careful selection of cases, it nevertheless offers a very useful and effective means of treatment.

Irradiation is indicated as the *method of choice* in the following groups:

1. Patients with mild to moderate hyperthyroidism, with slight or soft goiters, little weight loss, and without organic complications such as heart failure, arrhythmias, diabetes, hypertension and nephritis. Satisfactory results may be anticipated in about 85 per cent of such cases.

2. Prepubertal children with toxic diffuse goiter. Twenty-one such cases in children below the age of fifteen have been treated in our clinic in the past sixteen years with only one failure.

3. Postoperative recurrences of hyperthyroidism which cannot be controlled by iodine.

4. Patients who refuse operation.

5. Patients who present too grave surgical risks. Most of these can be improved sufficiently by irradiation to permit successful thyroidectomy.

6. Patients with severe or rapidly progressing ophthalmopathy.

The *advantages* of irradiation are: (a) low mortality and morbidity, (b) widespread availability, (c) minimal economic disability, (d) absence of discomfort and psychic trauma. Its

disadvantages are: (a) effectiveness generally less than that of thyroidectomy, and (b) the necessity of prolonged therapy (often four to six months) before its effect can be evaluated.

The *technic* employed in our clinic involves the daily delivery of 100 to 200 r units through one to three anterior portals for four to six days. This series of treatments is repeated every four to six weeks. Our patients who responded favorably received an average total dose of 2160 r units delivered in an average of 5.4 series. The patient's general condition and basal metabolic rate should be checked at least once a month during treatment. Many mild cases can be treated without interrupting the patient's work.

Complications of irradiation are rarely important. They include esophagitis, laryngotracheitis, acute mediastinopericardial reactions, telangiectases, nausea and anorexia, and sometimes mild temporary exacerbations of the thyrotoxicosis. In some patients, the disease increases rather rapidly and continuously in severity after irradiation is begun. In such cases, treatment should be stopped and preparation for thyroidectomy instituted. It is advisable not to give iodine to patients receiving irradiation. The statement is frequently made that thyroidectomy is made more difficult by previous irradiation of the thyroid because of increased vascularity of the gland and the formation of pericapsular adhesions. We seriously doubt the truth of this statement. In only a few instances have any of our patients shown evidence of such adhesions. In these instances, the adhesions were light and relatively nonvascular, and gave the surgeon no real trouble.

**THYROIDECTOMY.**—Thyroidectomy remains as the most generally effective method of treating hyperthyroidism, *when properly performed by an experienced surgeon after careful preparation*. Thyroidectomy is indicated: (1) in all severely toxic or rapidly progressive cases, with the possible exception of those showing marked or increasing ophthalmopathy; (2) in thyrotoxicosis complicated by cardiac arrhythmia, congestive failure, angina pectoris, diabetes, marked malnutrition or other disease, except when special contraindications exist; (3) in patients with toxic nodular goiter; (4) in milder cases which do not respond to irradiation or other conservative therapy. The *mortality* of thyroidectomy has been greatly reduced by the preoperative use of iodine begun in 1922 by H. S. Plummer: by better understanding of preoperative treatment and the optimal time for operation; by improving teamwork between surgeon and internist, and by the intel-

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**THYROIDECTOMY.**—Thyroidectomy remains as the most generally effective method of treating hyperthyroidism, *when properly performed by an experienced surgeon after careful preparation*. Thyroidectomy is indicated: (1) in all severely toxic or rapidly progressive cases, with the possible exception of those showing marked or increasing ophthalmopathy; (2) in thyrotoxicosis complicated by cardiac arrhythmia, congestive failure, angina pectoris, diabetes, marked malnutrition or other disease, except when special contraindications exist; (3) in patients with toxic nodular goiter; (4) in milder cases which do not respond to irradiation or other conservative therapy. The *mortality* of thyroidectomy has been greatly reduced by the preoperative use of iodine begun in 1922 by H. S. Plummer; by better understanding of preoperative treatment and the optimal time for operation; by improving teamwork between surgeon and internist, and by the intel-

ligent use of the two-stage operation. In well organized clinics, operative mortality in uncomplicated hyperthyroidism should not exceed 1 per cent. In cases complicated by heart failure, a mortality rate between 5 and 8 per cent must be anticipated. In the hands of the occasional or inexperienced thyroid surgeon, the postoperative death rate will probably average 8 to 10 per cent in uncomplicated cases. The selection of an experienced surgeon, therefore, is of utmost importance. Thyroidectomy should be regarded as an incident, albeit a very important one, in the course of thyrotoxicosis. Prolonged supervision for at least two and preferably five years after operation is essential for the detection of recurrence or postoperative hypothyroidism.

The proper *preoperative regimen* may be outlined as follows: In uncomplicated cases, the patient should be allowed out of bed for two or three hours daily. The diet should be as high as possible in caloric content (not less than 3000 calories daily) and should contain about 1.25 gm. of protein per kilogram of ideal body weight, 80 to 100 gm. of fat and the remainder in carbohydrate. Attractive physical environment and pleasant, tactful medical attendants are very helpful. Extra amounts of vitamin B complex should be given. Small doses of insulin (5 to 10 units before meals) may be helpful in patients with anorexia. We have employed feeding by intestinal tube with success in a few patients whose weight could not otherwise be increased. Moderate sedation may be given in the form of barbiturates such as phenobarbital,  $\frac{1}{4}$  to 1 grain three times daily, with additional sedation at bedtime. Iodine may be given in the form of Lugol's solution or saturated solution of potassium iodide, minims 10 three times daily. A moderate amount of diversion (visitors, reading, cards, sewing, etc.) is desirable. When possible, the patient should be kept from contact with postoperative patients. The preoperative treatment should preferably be carried out in the medical ward, and the patient should be sent directly from there to the operating room. Occasionally, however, contact with a successfully operated patient will help the morale of an apprehensive subject. The old method of anoci-association ("stealing the thyroid") is still occasionally useful.

The basal metabolic rate should be determined about every third day as its trend is helpful in the selection of the time for operation. Some clinicians,<sup>16</sup> however, no longer regard the time of maximal decrease in basal metabolism as the optimal time for operation, but are content to wait for a week or ten days after this point is reached.

The major criteria in determining operability are, in the order of their importance: (1) the weight curve, (2) the patient's mental attitude, (3) the pulse rate and (4) the basal metabolic rate. Patients who do not eat well, who do not gain weight, and who remain apprehensive and fearful of operation are not good surgical risks and produce the majority of the unfavorable postoperative reactions. If the patient is eating well, gaining weight, and anticipates the operation without fear, failure of the pulse rate and metabolic rate to drop need not be too seriously regarded. Thyroidectomy is never an emergency operation. Disaster results more often from operating too soon after hospitalization than from waiting too long. Thompson<sup>17</sup> has recently emphasized the importance of a careful search for beginning respiratory infection or a sudden increase in the severity of the hyperthyroidism on the day before operation. He also advises a large carbohydrate meal with a dose of iodine six to eight hours before operation.

#### Treatment of the Thyroid Crisis

This grave complication of hyperthyroidism, the cause of which remains obscure, may occur spontaneously, after psychic or emotional shock, physical trauma, surgical operations or acute infections. It is commonest, however, after thyroidectomy. It is characterized by rising temperature and heart rate, restlessness, nausea and vomiting, diarrhea, delirium, and finally in about 90 per cent of the cases by coma and death. Extreme hyperpyrexia is common. Treatment must obviously be heroic. Ice packs, ice water enemas, oxygen, intravenous glucose, saline and whole blood, digitalis and morphine have all been recommended. Some clinicians condemn the use of iodine, but it is our practice to use it in fairly large doses (2 to 4 gm. of sodium iodide intravenously per day). The parenteral administration of large doses of



thiamine and nicotinic acid is also indicated. The incidence of postoperative thyroid crises can be kept at a minimum by proper preoperative preparation.

#### Treatment of Thyrotoxic Heart Failure

This is based in general upon the same principles which govern the treatment of heart failure from other causes, with the following differences: (1) Thyrotoxic patients are usually somewhat more tolerant to digitalis than other cardiac patients. This is especially true of the occasional younger patients who develop "pure" thyrotoxic heart failure. (2) Iodine helps to relieve the demands on the circulation by lowering the metabolic rate and hence the nutritional requirements of the entire body, including the myocardium itself. (3) It is better to postpone thyroidectomy until cardiac compensation has been restored, if this can be accomplished by medical measures alone. In some cases, however, compensation cannot be restored until the goiter has been removed, and these patients must of course be operated upon while congestive phenomena still persist. The operative risk is somewhat increased in such patients and selection of the optimal time for operation calls for considerable clinical judgment and experience. Many patients who have shown normal cardiac rhythm before operation will go into auricular fibrillation for a few days after operation. This is of no particular importance. The postoperative disappearance of established fibrillation depends somewhat upon the duration of the arrhythmia. In general, about 50 per cent of such patients will revert to normal rhythm after thyroidectomy. Our own experience with quinidine in the treatment of auricular fibrillation has not been very gratifying.

#### Treatment of Hyperthyroidism in Pregnancy

Opinion varies rather widely upon this subject. It is our belief that thyroidectomy increases somewhat the risk of abortion or miscarriage. In many instances hyperthyroidism appearing during pregnancy will diminish in intensity or disappear entirely after delivery. It does not seem wise to apply therapeutic generalizations under such circumstances, but to

treat each case individually. Mild cases may often be treated satisfactorily by irradiation. If such conservative therapy be employed, iodization just before term may prevent an acute exacerbation of the disease after delivery. If the thyrotoxicosis becomes progressively worse, thyroidectomy may be necessary at any stage of gestation.

#### Treatment of Hyperthyroidism Complicated by Ophthalmopathy

The term "ophthalmopathy" has been used by Means and his associates<sup>18</sup> to include exophthalmos, ophthalmoplegia, edema and congestion of the episcleral tissues, conjunctiva and lids, as well as degenerative changes and cellular infiltration involving the extraocular muscles and the tissues of the orbit. This ocular syndrome is often associated with hyperthyroidism. An interesting trend of thought has been developed in recent years<sup>19</sup> leading to the conclusion that ophthalmopathy and hyperthyroidism are not directly related etiologically. There is considerable evidence to implicate dysfunction of the anterior pituitary in the production of ophthalmopathy. There is likewise evidence to suggest that the presence of the thyroid may actually tend to inhibit progression of the ocular changes. In some instances, ophthalmopathy progresses rapidly after thyroidectomy, or may indeed first appear after such an operation. Similar eye changes may occur in persons with myxedema or with normal thyroid function. Some clinicians at present therefore refrain from thyroidectomy in thyrotoxicosis associated with severe or rapidly progressive ophthalmopathy. Instead, irradiation, iodine and desiccated thyroid (in patients whose basal metabolism falls to substandard levels during treatment) have been used. Irradiation of the pituitary and orbital areas has also been recommended. This concept is relatively new and not yet generally recognized by physicians, but it represents an interesting and important modification of previous therapeutic principles.

#### Use of Iodine in Hyperthyroidism

The misuse of iodine in thyroid disease is one of the commonest mistakes in medical practice. Its chief abuse is in its

prolonged administration to thyrotoxic patients, with the result that the patient becomes iodine "fast." When thyroidectomy finally becomes imperative, proper preparation is no longer possible and the surgical risk is greatly increased. The following statements, therefore, deserve particular emphasis:

1. Iodine in any absorbable form will produce objective and subjective improvement in about 97 per cent of thyrotoxic patients. The remainder are either unimproved or actually grow worse under its use.

2. In about 90 per cent of patients who respond to iodine, such response is rather gradual and lasts for only a few weeks; thereafter the disease slowly regains its previous intensity, and refractoriness to further iodization develops.

3. In about 10 per cent of patients who respond to iodine, the response is prompt and marked, the basal metabolic rate often dropping abruptly below the normal zone. In such patients, the disease may usually be kept under control until permanent remission occurs. The choice of iodine as the chief therapeutic agent under these circumstances, however, requires considerable experience and judgment.

4. Sensitivity to iodine is not uncommon in thyrotoxic patients<sup>20</sup> and may occasionally cause death.

5. The principal *indications* for the use of iodine in hyperthyroidism are: (a) in preparing the patient for thyroidectomy, (b) during the immediate postoperative period, (c) in the treatment of thyroid crisis, (d) in the treatment of postoperative recurrences of hyperthyroidism, (e) as a diagnostic test in doubtful cases, and (f) as a major therapeutic agent in certain *carefully selected* mild cases, patients who show a marked, prompt response to iodization, and patients with marked or rapidly progressive ophthalmopathy.

#### NONTOXIC DIFFUSE GOITER

##### Diagnosis

The diagnosis of diffuse goiter seldom presents any difficulties. However, subcutaneous fat is occasionally mistaken for thyroid enlargement. In palpating the thyroid gland it is best to stand behind the patient with the thumbs toward the back of the neck and the fingers on either side of the trachea.

The patient is then asked to swallow. As the thyroid rises its size, shape and consistency can be roughly determined. *Unless the examiner can definitely feel the entire lower border of the gland as it reaches its highest point during deglutition, the possibility of substernal extension cannot be excluded.* Pedunculated extensions of thyroid tissue may be encountered in various bizarre positions—intrathoracically, laterally in the neck, between the trachea and esophagus, or even behind the esophagus. These are usually detected only at operation.

### Treatment

The prophylactic value of iodized salt, iodization of water supply, or the semi-annual administration of small doses of iodide (0.2 gm. of potassium iodide daily for ten days) in reducing the incidence of goiter in endemic areas has been thoroughly established since the pioneer work of Marine and Kimball in 1917. The continued frequent occurrence of such goiters in nonendemic areas is attested, however, by the fact that 1540 cases have been encountered in our Endocrine Clinic in the past sixteen years. Since the development of hyperthyroidism, nodularity or malignancy is uncommon in nontoxic diffuse goiter in nonendemic areas, the prognosis is generally favorable. The complete disappearance of such goiters under medical treatment, however, is uncommon. If there is evidence of coexisting hypothyroidism, the use of desiccated thyroid substance is indicated. Likewise, the administration of small doses of iodine is justified in an attempt to reduce the size of the goiter or to prevent further increase.

The method employed in our clinic is as follows: The patient is given by mouth 5 minims (0.3 cc.) daily of a saturated solution of potassium iodide. The symptoms of iodine sensitivity are explained to the patient and he is instructed to report any such developments promptly. If no such sensitivity is present, the iodide is continued during alternate months, until three monthly courses have been received. If the goiter has not decreased in size by this time, it is concluded that no response to such treatment can be expected and thereafter only semi-annual prophylactic doses of iodide are given, using the dosage mentioned above. The patient is examined every six months to determine any change in the status of the goiter. If reduction in size of the thyroid follows the administration of iodide, this therapy is continued during alternate months until no further

reduction in size occurs. Thereafter semi-annual prophylactic doses are continued. In our experience some response to iodide therapy in nontoxic diffuse goiter may be anticipated in about 30 per cent of cases.

Much has been written about so-called iodine-induced hyperthyroidism occurring in patients receiving iodine for nontoxic goiter. While it is true that hyperthyroidism occasionally appears in such patients, the same complication also occurs in many patients with nontoxic goiters who have not received iodine. The factor of coincidence seems impossible to exclude. Our own experience does not permit us to accept the concept that a nontoxic goiter may be stimulated to toxicity by the administration of iodine.

Diffuse nontoxic goiters which do not respond to iodide therapy and which become nodular, cosmetically undesirable or cause pressure symptoms in the neck or mediastinum should be removed by subtotal thyroidectomy. Except in certain cases of malignancy, irradiation therapy is useless in nontoxic goiter whether diffuse or nodular. The parenteral administration of the thyrotropic factor of the anterior pituitary has been tried in nontoxic diffuse goiter with indifferent results.

#### NONTOXIC NODULAR GOITER

##### Diagnosis

Nodular enlargement of the thyroid may be confused with several other lesions in the neck and mediastinum. These include lymph node enlargements from a variety of causes (metastases, tuberculosis, lymphosarcoma, Hodgkin's disease, and so forth), aneurysms of the aorta, subclavian or innominate arteries, branchial or thyroglossal cysts, cystic hygromas, laryngeal cysts, diverticula of the esophagus and a variety of mediastinal tumors. In hypertensive subjects the presence of an abnormally pulsatile innominate artery in the supra-sternal notch is frequently mistaken for nodular enlargement of the thyroid isthmus. Large substernal goiters may present only small portions of their total mass, above the clavicles or manubrium. These protrusions may be so small as to be palpated only with difficulty. In rare instances the entire thyroid gland lies within the thorax. Aberrant masses of thyroid tissue of varying size unconnected with the thyroid gland itself

may be found anywhere in the neck or mediastinum. When occurring in the neck they are often mistaken for lymph nodes.

The term "adenoma" is often loosely applied to any nodular enlargement of the thyroid. This is obviously unjustifiable, since the histologic nature of the mass cannot be determined by palpation. As a matter of fact, *true adenomas* probably comprise only a fraction (perhaps 10 per cent) of all thyroid nodules. The remainder consist of localized areas of hyperinvolution often with pseudocapsule formation and a variety of secondary degenerative changes, such as cyst formation, hemorrhage and calcification.

The early diagnosis of *malignancy of the thyroid* is difficult. Only too often the process has metastasized or extended hopelessly beyond the capsule of the gland before the diagnosis is suspected. Any thyroid enlargement, whether nodular or diffuse, which grows rapidly or is associated with fixity of the gland should be suspected of malignancy. Induration and recurrent laryngeal nerve paralysis, which are regarded by some clinicians as important diagnostic criteria, have not in our experience been particularly reliable. Calcification occasionally occurs along with malignant disease of the thyroid. It is sometimes difficult to differentiate between malignant disease and chronic thyroiditis of the Hashimoto (struma lymphomatosa) or Riedel (ligneous) types, especially since the latter may occasionally produce fixity of the gland. In case of doubt it is better to regard the lesion as malignant.

*Acute or subacute nonsuppurative thyroiditis* may occur without apparent cause or following upper respiratory infection. There is often fever and leukocytosis and the gland becomes painful and tender. The enlargement occurs rapidly; it may be diffuse or limited to one lobe. Transitory signs of hyperthyroidism may occur. The prognosis is good with conservative treatment (small doses of iodide, analgesics, external application of cold). In subacute cases lasting for several weeks the exclusion of a rapidly growing neoplasm may be difficult.

Rapidly progressive localized enlargements of the thyroid

may result from *abscess* or *hemorrhage* into the gland. Hemorrhage is usually preceded by trauma but may occur spontaneously in arteriosclerotic persons. Both hemorrhage and abscess are associated with tenderness, but the latter is usually accompanied by greater fever and leukocytosis. Transitory, relatively acute, sometimes tender diffuse enlargement of the thyroid occasionally occurs during the administration of thiocyanates for the treatment of hypertension. Temporary hypothyroidism may accompany such enlargement.

### Treatment

Nontoxic nodular goiter is primarily a surgical problem. Medical treatment is of no avail and irradiation is indicated only in inoperable malignancy or after the removal of a malignant tumor. Nodular goiters are potentially dangerous for the following reasons: (1) About 60 per cent of them eventually become toxic. This toxicity usually develops insidiously and is less apt to undergo spontaneous remission than in primary diffuse toxic goiter. (2) About 2 to 3 per cent of nodular goiters prove to be malignant. Conversely, about 97 per cent of carcinomas of the thyroid arise from nodular goiters. (3) Many of those which do not become toxic or malignant increase progressively in size, often extending into the thorax, and produce dangerous pressure upon the trachea, esophagus or other mediastinal structures. (4) There is some evidence, not yet conclusive, which suggests that nodular goiter may at times cause cardiac damage without producing the typical picture of hyperthyroidism.

The *prophylactic surgical removal* of all nodular thyroid enlargements therefore appears justifiable. One is occasionally tempted to allow small, soft localized masses to remain under observation. Even this degree of conservatism is theoretically unwarranted, since the presence of early malignant change cannot be excluded in any nodular goiter. If all nontoxic nodular goiters could be removed surgically the incidence of hyperthyroidism would be greatly reduced and that of carcinoma of the thyroid almost eliminated.

The suspected presence of malignancy of the thyroid calls for *total thyroidectomy* unless there is obvious evidence of

metastasis or extension beyond the capsule of the gland. If the lesion be inoperable palliative irradiation may be undertaken cautiously. Acute swelling of the carcinomatous thyroid following irradiation occasionally requires emergency tracheotomy. The type of operation required in benign nontoxic nodular goiter depends upon the size, number and location of the nodules. If only a single nodule be present and the remainder of the gland be normal, simple enucleation of the nodular mass may be sufficient. The same procedure may suffice even though the remainder of the gland presents a moderate diffuse enlargement. Where the gland is studded with multiple nodules, subtotal resection is indicated.

No particular medical preparation of the patient is necessary before operation for nontoxic goiter. In competent surgical hands the mortality should be very low (not over 0.5 per cent). The principal causes of the occasional operative deaths are pneumonia and other infections, hemorrhage, and unpredictable cardiac collapse.

#### SUMMARY AND CONCLUSIONS

This review of the more important aspects of the diagnosis and treatment of the principal diseases of the thyroid has, of necessity, been relatively brief. An attempt has been made to emphasize those features which have seemed most important from the clinical point of view. In summary it may be justifiable to stress again a few of the points which may prove most helpful to the practitioner in dealing with thyroid problems. These may be stated as follows:

1. Hypothyroidism often masquerades in a variety of clinical disguises.
2. The optimal dose of desiccated thyroid varies from patient to patient.
3. The same brand of thyroid substance should be used throughout the course of any given case.
4. The treatment of hypothyroidism should not be abandoned because of the appearance of signs of overdosage.
5. Hyperthyroidism often simulates other diseases and other diseases may simulate hyperthyroidism.
6. Subtotal thyroidectomy competently performed after



proper preparation is the best single method of treating hyperthyroidism. Irradiation is useful in carefully selected cases.

7. The beneficial effect of iodine in hyperthyroidism is usually temporary. The principal use of this drug should be in the preparation of patients for thyroidectomy.

8. Nontoxic diffuse goiter seldom responds completely to iodine therapy, but such therapy is justifiable because of its occasional good results and possible prophylactic effect.

9. Nontoxic nodular goiters should be treated surgically unless special contraindications exist.

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## DIAGNOSIS AND SURGICAL TREATMENT OF GOITER\*

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and

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WE propose to limit our present discussion to the common types of thyroid disorders, colloid goiter, diffuse toxic goiter, nodular goiter (adenomas) with and without toxic change, and inflammatory goiter.

### DIFFUSE TOXIC GOITER

#### Case I. Exophthalmic Goiter; Pre-existing Colloid Goiter Activated by Iodine Overdosage

Our first case for presentation is that of a young white woman. We first saw her in 1936 when she was twenty-eight years old. At that time she complained of dyspnea, palpitation, emotional instability, and loss of weight. The symptoms were all severe and of four or five months' duration. A goiter, which had been present since the age of sixteen, had become increasingly prominent in the past five months. The symptoms mentioned had all been present in a less acute form for approximately twelve years. When they first appeared a doctor told her she had a goiter and gave her iodine for a few months. Symptoms of acute hyperthyroidism followed.

Examination showed a thyroid gland which was diffusely enlarged. Exophthalmos was present. The pulse rate was 132 and the blood pressure in millimeters of mercury was 136 systolic and 68 diastolic. The heart action was forceful. A capillary pulse could be demonstrated in the nail beds. The patient was exceedingly nervous, very self-conscious, and her voice had a tremulous quality. She weighed 112 pounds. The basal metabolic rate was  $\div 65$  per cent.

After a period of preparation, bilateral subtotal thyroidectomy was performed on October 1, 1936. Sixty grams of hyperplastic thyroid gland were removed. Recovery was uncomplicated. The basal metabolic rate after operation was  $\div 10$  per cent.

Six years have passed since the operation. The patient has carried on a

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### Preoperative Preparation in Hyperthyroidism

The preoperative preparation of patients with hyperthyroidism is important. Essentially, it consists of a high caloric, high vitamin diet, iodine administration, and rest. We like to see our patients ingest 5000 calories a day, if possible. Fruit juices are given liberally, and furnish an excellent source of vitamin C in addition to their calories. One or two vitamin B complex capsules are given with each meal. These tablets contain 333 units of vitamin B<sub>1</sub>, 500 micrograms of riboflavin, 10 mg. of nicotinic acid, 130 micrograms of vitamin B<sub>2</sub>, and 170 micrograms of pantothenic acid. Iodine is given in the form of Lugol's solution, 10 to 15 minims three times daily. Patients are usually kept in bed, although this is not a hard and fast rule. Elderly patients do better if they sit out of bed in a chair for a few hours each day, and an occasional emotional, severely toxic patient will be quieter and happier if he is allowed to get up for a short period each day. Frequently patients require sedation and for this purpose we prefer the bromide elixirs, in doses of 5 to 10 cc. three times daily. When bromides are given we like to give the first dose just before noon, the second in the midafternoon, and the third an hour or two after the evening meal. Seven to twelve days of preparation is the average time. Just as the initial basal metabolic rate is only one index of toxicity, a fall in the rate is only one of the manifestations of response to treatment. A patient is ready for operation when the pulse rate falls and levels off at a relatively lower level, when he shows a gain in weight, and when examination of the gland indicates involution.

### Postoperative Care in Hyperthyroidism

Postoperatively, we commonly give 5 cc. of Lugol's solution by rectum when the patient returns to the floor. As soon as the patient is conscious he is placed in a sitting position in bed. Morphine sulfate, grain  $\frac{1}{6}$ , is given every three hours unless the respiratory rate falls to 16, and this dosage is maintained for twenty-four to forty-eight hours. In the first twenty-four hours 3500 cc. of parenteral fluid, of which 1500 cc. are normal salt solution, is given intravenously.

normal, active life in her community. Although she had been married for five years before operation, she had not become pregnant. Approximately one year after operation she became pregnant and was uneventfully delivered of a normal child. She weighs 132 pounds, her pulse rate is 82, and her blood pressure in millimeters of mercury is 118 systolic and 76 diastolic.

The diagnosis of exophthalmic goiter in this case was clear. Among other characteristic features was the increase in pulse pressure with its attendant capillary pulsation. An increase in pulse pressure usually accompanies severe toxicity. After operation a return to normal should occur. In this case there was a blood pressure change in millimeters of mercury from 136 systolic and 68 diastolic to 118 and 76, respectively, accompanied by a fall in pulse rate from 132 to 82. The patient is representative of many individuals all over the country who have hyperthyroidism, whose family physicians have made a proper diagnosis, and who return to their communities as useful citizens after thyroidectomy.

The early use of iodine in this case calls for special comment. When the patient was a girl of sixteen, a doctor told her she had a goiter and gave her iodine for a few months. Symptoms of hyperthyroidism followed. In all probability the lesion present at that time was a simple colloid goiter which was activated by iodine overdosage. Simple colloid goiter usually develops at or about the time of adolescence. As is well known, it is found most frequently in the goiter zones. Prophylaxis consists of administering a 10-mg. iodine tablet once a week or instructing the patient to use iodized salt. The average individual using iodized salt ingests 8 mg. of iodine a week. Prophylaxis has been used with marked success in the Great Lakes region and other areas where goiter is endemic. Once established, a colloid goiter should never be treated by large doses of iodine, for fear of activation similar to that in the instance just discussed.

We believe that colloid goiters should be operated upon. Judgment must of course be exercised; for the slight enlargement often seen at the time of puberty is usually only temporary. Large goiters are not only undesirable for cosmetic reasons but constitute a source of potential danger from toxic or degenerative changes.

Eight weeks after operation the patient was readmitted for the second stage. The time interval is somewhat longer than usual. On readmission the pulse was 96, the basal metabolic rate +27 per cent, and she had gained 13 pounds. Left subtotal hemithyroidectomy was done, 50 gm. of hyperplastic gland being removed. Although the throat was negative before operation, recovery was complicated by acute follicular tonsillitis. The patient was discharged ten days after operation. A month later, tonsillectomy was performed and recovery was uneventful. The basal metabolic rate at that time was +1 per cent.

This case illustrates two principles of treatment. First, the *danger of acute infection* arising during hyperthyroidism is shown by the severe reaction to the initial attack of tonsillitis. Thyroid crisis was imminent. Fortunately, iodine and other preparation had been carried out for nine days and the patient had not received any iodine before coming to the hospital. Fortunately, too, sulfanilamide was available. Drainage of the peritonsillar abscess was indicated. Similarly, operations for acute appendicitis and other emergencies are indicated during thyrotoxicosis. However, when thyrotoxicosis co-exists with other, nonemergency illnesses, the treatment of the thyroid disorder receives precedence. It is not unknown for postoperative hernia or gallbladder patients to go into thyroid crises on the second or third postoperative day. Such occurrences can be prevented by being on the alert to recognize symptoms of hyperthyroidism and to make the proper investigations before doing elective surgery.

The second principle illustrated is the importance of doing *stage operations* where toxic goiter is complicated by an infectious process. The presence of infection greatly heightens toxicity. Other instances in which stage operations should be considered are in patients over sixty years of age, in patients who have had toxic symptoms over a year, in patients who have lost considerable weight, and in patients who have become iodine fast. In addition to the factor of infection, the patient just discussed had lost 60 pounds in weight during two years of active symptoms.

#### TOXIC AND NONTOXIC NODULAR GOITER (ADENOMAS)

Adenomas of the thyroid can be divided into three classes: fetal adenoma, colloid adenoma, and papilliferous cystad-



Glucose in quantities of 200 to 350 gm. is given intravenously. Ice caps are applied to the head and precordium. The oxygen tent is used frequently. The tent is usually preferred to the B.L.B. mask because of its general cooling effect. Tincture of benzoin inhalations are given frequently during the first three days. On the day after operation, Lugol's solution by mouth is resumed and continued during the patient's stay in the hospital. Thereafter no more iodine is given. Fluids by mouth are begun as soon as the patient can drink and the diet is rapidly built up to the preoperative level. Most patients leave the hospital seven to ten days after the operation. They are instructed to lead a quiet, well regulated life for at least three months, when they return for a follow-up visit.

#### Case II. Diffuse Toxic Goiter, Illustrating Dangers of Acute Infections Arising during Hyperthyroidism and the Importance of Stage Operations

The next patient is a fifty-four-year-old woman whom we saw four years ago. At that time she complained of nervousness, palpitation, intolerance of heat and a swelling in the neck for two years. For several months amenorrhea, ankle edema and hoarseness were also present. During the two years of active symptoms she had lost 60 pounds in weight.

She was exceedingly nervous and apprehensive. Exophthalmos was present. The thyroid gland was enlarged bilaterally, the right side being somewhat more prominent than the left. Bruit was present. The pulse rate was 124 and the blood pressure in millimeters of mercury was 168 systolic and 78 diastolic. The basal metabolic rate was +81 per cent. She weighed 157 pounds. A diagnosis of diffuse toxic goiter was made and the patient was prepared for operation. This was an instance of late diagnosis, but fortunately no iodine had been given.

Nine days after admission to the hospital, the pulse had fallen to 84 and the basal metabolic rate to +39 per cent. On the tenth day the patient developed a severe tonsillitis and, after a chill, her temperature rose to 104° F. A throat culture showed hemolytic streptococci; a blood culture showed no growth. Full doses of iodine were continued, a 5000 calorie diet was maintained, and sulfanilamide treatment was begun. On the fifteenth hospital day a peritonsillar abscess was incised, with release of a large amount of pus. Five days thereafter the tonsillitis had subsided. The patient had lost 12 pounds and her pulse rate had risen from 84 to 100.

By the twenty-eighth hospital day the pulse had become stable at 80, the patient had regained 2 pounds, and the basal metabolic rate was +28 per cent. Right subtotal hemithyroidectomy was performed. Sixty grams of hyperplastic tissue were removed, comprising seven-eighths of the right lobe, the isthmus and the pyramidal lobe. Recovery was uncomplicated, and the patient was discharged on the eleventh postoperative day. Lugol's solution, 10 minims three times a day, a high caloric diet and vitamin B complex were continued.

*Fetal adenomas* are characterized by small cells resembling those found in fetal life. The capsule is usually definite and there is compression of the surrounding tissue. Colloid adenomas show large alveoli distended with colloid. When toxic, the cells are characteristically smaller and contain less colloid. Any single colloid adenoma may contain cells of all types. A papilliferous cystadenoma may represent nonmalignant degeneration of a colloid adenoma, but may show its characteristic structure from the start. Adenomas may be regarded as benign tumors of the thyroid gland and as such they are subject to growth, to necrosis, to hemorrhage and sometimes to malignant degeneration.

The nodular goiter contains numerous hypertrophied areas. In general, these nodules show pathological changes similar to colloid adenomas. Their surrounding stroma is dense and the thyroid tissue between them is compressed to an extreme degree. These are the tumors which account for large pendulous goiters and substernal goiters. We feel that nodular goiter, if nontoxic, should be operated upon to prevent the complications of growth, pressure symptoms, toxicity, necrosis and occasional malignant change. The operation is one of election but, even so, procrastination on the part of the patient must be overcome. Patients with toxic nodular goiter should be prepared for operation at once and should be operated upon when they are in fit condition. The preparation follows the same general plan as in diffuse toxic goiter, but often takes a few more days.

Mention should be made of *menopausal symptoms* which often accompany hyperthyroidism. We do not mean amenorrhea alone which is a common symptom, but rather hot flushes with amenorrhea occurring in women of menopausal age. The nervous symptoms of the menopause so closely resemble those of hyperthyroidism that the two states may occasionally be confused. In this situation the basal metabolic rate and occasionally a diagnostic course of Lugol's solution are of value in differentiating the two conditions. In a certain number of cases, however, thyrotoxicosis, usually in the form of toxic nodular goiter, and the menopause will co-exist. When they do, we feel both conditions should be treated. In

enoma. The classification is a pathological differentiation; for it is rare that one can make the exact diagnosis clinically. Adenomas per se may be regarded as discrete autonomous tumors, which usually are nontoxic. The diffuse nodular goiter, on the other hand, represents focal hypertrophy at numerous points within the gland, often on the basis of a pre-existing colloid goiter.

The *clinical findings* in nodular goiter are well known. If single, a discrete rounded tumor is found in either lobe or, more rarely, in the isthmus. The remainder of the gland is not enlarged. Multiple nodules produce greater distortion of the gland, depending upon their size and number. Nodular goiter usually is found in an older group of patients than those exhibiting diffuse toxic goiter. When toxic nodular goiter is present, exophthalmos is rarely found and the response to iodine treatment is less satisfactory than in diffuse toxic goiter. The operative mortality rates for patients with toxic nodular goiter are higher than for patients with exophthalmic goiter. As has been mentioned, adenomas occur in older patients, many of whom have already developed degenerative diseases of the cardiovascular, hepaticorenal and pulmonary systems. The progress of the disease is more insidious, and the toxic changes may be present for several years before the patient is brought to surgery.

*Toxicity* is usually manifested by the general effects of nervousness, loss of weight and intolerance to heat. In addition, the cardiovascular system often shows severe effects such as rapid pulse, elevated blood pressure, and fibrillation. Fibrillation may be intermittent, the heart resuming normal rhythm without medication. When the heart fibrillates in this way a toxic nodular goiter or, more rarely, a diffuse toxic goiter, should be suspected. After surgery about 60 to 70 per cent of patients with fibrillation show a return to normal rhythm. Iodine administration is particularly fraught with danger; for in many nontoxic nodular goiters severe toxic changes have been induced by well meant but nonetheless meddlesome courses of iodine preparations. These patients should never receive iodine unless they are being prepared for surgery.

toxic nodular goiter as day from night. A safe operation, a short hospital stay, and an excellent prognosis can be offered these patients.

We insist that every patient for whom a thyroid operation is contemplated should have the *vocal cords* examined before and after operation. One or more basal metabolic determinations are usually required. An x-ray examination for substernal goiter should also be made, especially in patients with nodular goiter and in patients who exhibit pressure symptoms.

In operating for adenoma or nodular goiter, one has three procedures from which to choose: enucleation, lobectomy and subtotal thyroidectomy. We believe no hard and fast rules can be made. The entire gland should always be carefully explored. A discrete, single adenoma is ideally suited for *enucleation*. In cases similar to the one just mentioned where the adenoma fills an entire lobe, *subtotal lobectomy* is often a safer and technically simpler operation than enucleation. When several nodules are found in one lobe of the thyroid, a careful search will usually reveal one or more nodules in the other lobe. For such cases, *subtotal thyroidectomy* is recommended.

#### Case IV. Toxic Nodular Goiter, Illustrating Advantages of Stage Operation in Selected Cases

The next patient is a woman of sixty-two years who looks ten years older than her actual age. She came to us four months ago complaining of a lump in the left side of the neck. She gave an indefinite history of weight loss and nervousness of twelve to fourteen months' duration. Dyspnea on slight exertion and evening ankle edema had been noted for about three months. The patient was tense. The folds of her skin hung loosely, indicating recent weight loss. The thyroid gland was generally and irregularly enlarged, and a hard, well circumscribed mass about 4 cm. in diameter was present in the left lobe. She had no exophthalmos. A fine tremor of the fingers was very evident. The heart was moderately enlarged. Cardiac rhythm was normal. A short systolic aortic murmur was heard. The blood pressure in millimeters of mercury was 140 systolic and 85 diastolic. The basal metabolic rate was  $\pm 36$  per cent, the vocal cords moved normally, and x-ray examination showed a calcified nodule in the left lobe of the thyroid. A diagnosis of toxic nodular goiter was made and the patient was prepared for operation. It was thought that a two-stage operation would be necessary.

Eight days after entering the hospital the patient had gained 4 pounds, her pulse had slowed from 88 to 72, and the basal metabolic rate had fallen to  $\pm 22$  per cent. On the ninth hospital day, left lobectomy was performed.

addition to preparing the patient for operation, progynon-B or theelin in rather large doses are given. The dose varies with the individual and no set rule of therapy can be postulated. It should be remembered that patients with hyperthyroidism often require two to four times as much hormone before operation as they will need after operation. As yet we have had little experience with stilbestrol.

### Case III. Nontoxic Thyroid Adenoma, with Easy Postoperative Course

The next patient is a forty-four-year-old white woman who was admitted to the Lankenau Hospital last year. For eight years she knew she had a goiter. No symptoms of hyperthyroidism had ever been present. Nine months before admission she developed difficulty in swallowing which gradually became worse. Closer questioning revealed hoarseness and some difficulty in breathing of a few weeks' duration. There were no other complaints. She had not taken iodine. Examination showed a large, elastic tumor which filled the right lobe of the thyroid and extended medially across the midline of the neck. The tumor was roughly spherical and measured approximately 5 cm. in diameter. The patient's general condition was excellent. The pulse was 84, the blood pressure in millimeters of mercury was 130 systolic and 68 diastolic and the basal metabolic rate +3 per cent. She weighed 150 pounds. Examination of the vocal cords showed only congestion. There was no x-ray evidence of substernal thyroid enlargement.

A diagnosis of nontoxic thyroid adenoma was made, and the patient was operated upon the day after admission to the hospital. When the gland was exposed a large adenoma was found which occupied the entire right lobe. The isthmus and left lobe were normal. Right subtotal lobectomy was done, with removal of 60 gm. of thyroid gland. Recovery was entirely uneventful and she was discharged nine days after operation. This patient received no iodine during her hospital stay. Postoperative vocal cord examination showed normal motion of both cords. The pathological report was fetal adenoma.

At the present time the patient is in excellent health. The scar is inconspicuous, the remaining thyroid tissue shows no abnormalities, her pulse is 88, her blood pressure 128 systolic and 70 diastolic, and her weight 149 pounds.

This case illustrates a number of points, the most significant of which is the smooth, easy postoperative course which can be expected in nontoxic adenoma. The patient came to us to be relieved of pressure symptoms. There was no evidence of toxicity. Such a situation must, of course, be relieved surgically, but it should be emphasized that an operation for uncomplicated adenoma is as different from an operation for

## INFLAMMATORY GOITER (THYROIDITIS)

## Case V. Ligneous Thyroiditis Complicated by Dietary Deficiencies

The next patient, a woman of thirty-four, came to us for appendectomy and myomectomy in June, 1939. Her hospital stay was uneventful and at that time she had no thyroid symptoms and no enlargement of the thyroid.

In January, 1941, we saw her again. She complained of nervousness, precordial pains and palpitation. The symptoms were unrelated to exertion. There had been no weight loss. Her family doctor had given her an iodine preparation for seven weeks before we saw her. Examination showed a diffuse general enlargement of the thyroid with no thrill or bruit and no substernal extension. The blood pressure in millimeters of mercury was 140 systolic and 95 diastolic, and the pulse rate 72. No exophthalmos was present and there was no tremor of the fingers or tongue. The basal metabolic rate was  $+2$  per cent and when it was repeated four days later it was  $+4$  per cent. A careful history revealed nervousness, dietary deficiencies, especially in fruits and vegetables which she seldom or never ate. Since the diagnosis of the thyroid state was not clear-cut and since the dietary deficiency was marked, we decided to keep the patient under observation on an adequate high vitamin diet. No iodine was given. On this program she showed marked improvement, losing her nervousness, precordial pain and palpitation. She gained 12 pounds in weight. The thyroid gland remained enlarged at first but gradually became smaller and as it decreased in size it also became firmer than the average gland.

In August, 1941, the patient began to notice a feeling of oppression in the throat and chest. As this sensation became more marked, it could be reproduced by deep palpation of the thyroid gland. The basal metabolic rate was  $-8$  per cent, the blood pressure in millimeters of mercury was 130 systolic and 80 diastolic, and the pulse rate 84. The vocal cords moved normally. X-ray showed no substernal extension. A diagnosis of thyroiditis was made and on October 28, 1941, a subtotal thyroidectomy was done, with removal of 112 gm. of thyroid tissue. The gland tissue was firmer than normal. The pathological report was ligneous thyroiditis. Recovery was uneventful and the patient was discharged eight days after operation. The basal metabolic rate at that time was  $-13$  per cent. The vocal cords moved normally.

At the present time, the patient has no complaints. The pressure symptoms have gone, and the nervousness and precordial distress noted early in 1941 have not returned. The basal metabolic rate is  $-9$  per cent.

The case is cited to illustrate the importance of searching for nutritional disturbances in patients who may have toxic goiter and to stress the point that when a diagnosis of thyroid disease is uncertain, one should not operate before the clinical picture is clear.

There is more to the surgical treatment of thyroid disease than the various operative procedures. The menopausal factor has been mentioned. Undernourished persons may show

The patient's blood pressure before operation was, in millimeters of mercury, 130 systolic and 70 diastolic. Ten minutes after the operation was begun the pressure rose to 240 systolic and 120 diastolic. Fifteen minutes later, at the end of the operation, the pressure was 210 systolic and 110 diastolic. A rise in pressure of this magnitude confirmed the preoperative opinion that stage procedures were indicated. The pulse pressure, it will be noted, rose from 50 to 120. We feel that when blood pressure and pulse pressure show dramatic and sudden rises in the course of a thyroid operation, the operation should be terminated as expeditiously as possible. Usually lobectomy will be the procedure chosen; for, as in this case, one lobe will have been partially amputated when the change in circulation occurs.

In the case of this patient a smooth recovery followed the first stage. Pathological examination showed a large calcified adenoma and numerous smaller colloid adenomata with areas of involution and other areas of hyperplasia. Four weeks later right lobectomy was performed. The blood pressure this time varied between 140 systolic and 80 diastolic at the start and 160 systolic and 100 diastolic at the end of the operation. No significant pulse pressure changes occurred. The postoperative course was uneventful and the patient left the hospital ten days after the second operation. Pathological examination showed multiple colloid adenomata with areas of involution and other areas of hyperplasia.

The patient has gained 4 pounds; her nervousness and tremor are gone, and the basal metabolic rate is  $+12$  per cent. Laryngeal examination shows normal motion of both vocal cords.

The point of greatest interest brought out by this case is the smooth blood pressure and pulse pressure curve during the second operation. We are not advocates of frequent stage operations. However, stage operations have occupied a prominent place in recent surgical literature and their value has been properly stressed. It is generally accepted that in elderly patients who are in poor general condition, in patients who have had severe hyperthyroidism for over a year, in patients who have lost considerable weight (over 60 pounds), in patients with heart disease, the so-called thyrocardiacs, and in patients with infectious processes, stage procedures should be considered. As Lahey has often pointed out, the decision for or against stage procedures should be made when the patient is first seen, and not after preoperative preparation is well under way. There will be patients in whom a subtotal thyroidectomy is contemplated who show the circulatory disturbances manifested by this patient in her first operation. When this occurs, the operation must be terminated promptly if a fatality is to be avoided.

## DIAGNOSIS AND X-RAY TREATMENT OF HYPERTHYROIDISM

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HYPERTHYROIDISM is a condition which concerns especially the general practitioner, the endocrinologist, the ophthalmologist, the surgeon, the radiologist, and, in fact, enters at times, as a complicating factor, into almost every other branch of medicine. My interest in the x-ray treatment of hyperthyroidism dates from 1904, or about thirty-eight years ago, when I treated my first case.

Thousands of cases of hyperthyroidism have now been treated by irradiation and recorded by various authors (Borak, Ginsburg, Groover, Christie and Merritt, Harris, Holzkecht, Loucks, Menville, Belot et Ledine, Jenkinson, Hunter, and many others). I have myself written on this subject on eleven previous occasions.

The general practitioner is usually the first to come in contact with a case of hyperthyroidism. To him belongs the responsibility of making the diagnosis and its differentiation from other similar clinical syndromes, and he should remain in charge until the patient is restored to a normal condition, or, at least, until able to carry on in the usual occupation.

### SYMPTOMS AND DIAGNOSIS

The first essential in the diagnosis of hyperthyroidism is that the attending physician shall think of this possibility. In the advanced grades, the diagnosis is not difficult, but in the early stage or mild forms, one may have difficulty in arriving at a definite conclusion. In a fully developed exophthalmic goiter (Graves' or Basedow's disease), in which one finds prominent eyes, and other definite ocular symptoms, and

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symptoms which resemble those of hyperthyroidism and, conversely, in hyperthyroidism nutritional deficiencies are common. Looking back on the case of the patient just cited, it is obvious that thyroiditis was present from the start. At that time, however, the exact nature of the thyroid disease was *not definite*. There was no evidence of hyperthyroidism. We feel that nothing is lost and a great deal may be gained in such patients by keeping them under close clinical observation until the picture becomes clarified. If one operates hastily, a certain number of unnecessary operations will be performed. If hyperthyroidism develops while the patient is under observation, then of course the picture is clarified and operation should be done as soon as possible. Occasionally, as in this case, a diagnosis of thyroiditis will be made and operation will follow. The exception to the policy of observation is found in patients who are suspected of harboring a carcinoma of the thyroid. In such instances, operation should never be delayed.

#### SUMMARY

Cases have been presented to illustrate certain major points in the diagnosis and surgical management of thyroid disorders. The possible harmful effect of iodine administration has been stressed. The general methods of diagnosis, preparation, and postoperative care for colloid goiter, diffuse toxic goiter, nodular goiter, both toxic and nontoxic, and thyroiditis have been discussed. No attempt has been made to give the technical details of operative procedures. At the present time, definitive treatment of the great majority of thyroid disorders means surgical treatment. However, as has been said, there is more to the treatment of thyroid disease than operation alone. Cardiac, nutritional and endocrine factors call for close cooperation between internist and surgeon throughout the treatment of thyroid disease.

*Roentgen examination of the heart* in the earlier stages, and before cardiac degeneration, shows no enlargement, but does show excitability with rather violent contractions of the heart muscles.

*Goiter* is usually present and may occur as a general hyperplasia such as exists in exophthalmic goiter (Graves' or Basedow's disease), or the goiter may occur as single or multiple adenomas. Such adenomas when large are recognized by sight and palpation as a goiter, but when such adenomas are small, deeply seated, they may not be palpable, and of course not visible. The adenomatous goiter is not very vascular and in this respect differs from exophthalmic goiter. Thrills or bruits are rarely present. Adenomas which produce well marked symptoms usually occur in older women (often from forty to sixty years of age). Adenomatous goiter may produce mechanical pressure symptoms such as hoarseness, aphonia, cough, laryngeal stridor or tracheal wheeze.

*Roentgen Examination for Goiter.*—In 1921, I described a technic for the roentgen demonstration of goiter. The patient is placed in the standing position facing the film, his neck rotated to a semilateral position toward the affected side, or when there is doubt as to the side affected, examined in a similar position on both sides.

Roentgen examination has the advantage over mere external palpation in that it shows the amount of pressure on the trachea. The goiter may extend from the neck into the upper mediastinum in the *substernal region*, but there may be no visible or palpable goiter in the neck, and yet, such a lesion can be demonstrated by the roentgen rays, and only by the roentgen rays.

The goiter may be retro-esophageal and demonstrated only by the roentgen rays (Garlock). This is usually shown by a simple postero-anterior view of the chest, but occasionally it is an advantage to also make an oblique film of the upper mediastinum. One cannot rule out the presence of a goiter without a careful x-ray examination of the substernal region. I have seen failures from roentgen therapy because the treatment was given over the normal thyroid region instead of over the substernal goiter.

when the patient has a very definite goiter, asthenia, a rapid pulse, emaciation, sleeplessness, great irritability, and general exhaustion, the diagnosis can be made on sight. But, when only one or two of such symptoms are present, and especially when no exophthalmos or goiter is present, the diagnosis becomes difficult.

I am not using the term hyperthyroidism as being synonymous with exophthalmic goiter. Hyperthyroidism is a prominent and probably the leading symptom of exophthalmic goiter, but one may have a severe grade of hyperthyroidism without either exophthalmos or goiter. Furthermore, hyperthyroidism may be only a part of a general disturbance of the endocrine system. Basically, hyperthyroidism means an increase in the thyroid secretion. This increase may be due to a hyperplasia of the glandular tissue, or may be due to an overactivity of a normal amount of thyroid.

The cardinal symptoms of hyperthyroidism are referable to the cardiovascular, the muscular, the nervous and the gastro-intestinal systems.

*Tachycardia* is the outstanding cardiovascular symptom, and in itself when persistent, should make one think of hyperthyroidism. It is generally associated with marked instability of the heart so that a slight amount of exercise, such as walking back and forth across the room three or four times, will increase the pulse rate 20 to 30 or more beats, while the same amount of exercise in a normal person will cause an increase of only 10 beats; or the physician may take the pulse on the patient's arrival at the office, and then again after the patient has had a quiet rest. I have used this test during many years, not only to help in making a diagnosis but in checking the progress of the patient under treatment. The pulse is usually full and the patient may complain of a sensation of throbbing. In the advanced stages of the disease, certain arrhythmias commonly occur such as extrasystoles, and later *auricular fibrillation* with intermittent pulse, *myocardial degeneration* with decompensation, and, finally *cardiac failure* may ensue. The increased circulation may give rise to *thrills* or even *bruits* over the thyroid. Flushing and increased perspiration are common.

tomy. In every case in which this occurs, it will be found that there has been a persistence of the agents which were active in producing the primary hyperthyroidism—focal infection, social maladjustments, worry, overwork or some other strain."

It is well known that patients who are suffering from hyperthyroidism associated with a goiter postpone the consultation with their family physician for fear he or she will be sent to a surgeon for operation. To avoid such delays and to conserve the patient's energy it is, therefore, well to remember that irradiation therapy is approximately of equal value with surgery in the end-result, and if patients learn that not all cases must be operated upon, they will be less likely to delay consultation.

*In dealing with hyperthyroidism, we must assume that there is an overgrowth or a new growth of the thyroid gland, or a hyperfunction of the normal amount of glandular tissue.* The condition can be relieved by surgery and satisfactory results can be obtained if the surgeon removes just the right amount of tissue; or the disease can be controlled by irradiation which gradually reduces the activity of the cells, and causes an atrophy of the hypertrophic or hyperplastic tissue when present. This reduction in the activity of these cells takes place even when no known enlargement or tumor is present. By careful observation and basal metabolic rate control, one need not exceed the necessary dosage to bring the condition to normal. It is my practice to discontinue the treatment when the basal metabolic rate has reached approximately  $\pm 15$  per cent. It will probably gradually descend to normal.

#### Indications for Irradiation

On the basis of observations of myself and other radiologists, I believe that irradiation is indicated in most cases of hyperthyroidism in which the patient is not in crisis, or is not suffering from definite pressure symptoms. On the other hand, operation should be recommended in all simple or non-toxic goiters unless there is some contraindication, in which case a moderate amount of irradiation may be used. When

The *muscular symptoms* of hyperthyroidism consists of tremors of the hands and muscular fatigue after slight exertion. These symptoms are probably basically nervous in origin, and due in part to the increased metabolism.

The *nervous symptoms* consist of marked excitability, tremor, exhaustion after slight exertion, great sensitivity to heat and cold, and alternate flushing and blanching of the skin; the hands and feet are apt to be cold, clammy, and associated with increased perspiration. There may be mental symptoms varying from irritability to loss of control, fits of temper, loss of interest and concentration, and poor memory.

The *ocular signs and symptoms* consist of varying degrees of exophthalmos, widening of the slits, a staring expression, the incoordination of the eyeball and the eyelid when the patient follows an object in a downward direction (von Graefe's sign); the widening of the palpebral cleft (Stellwag's sign), with infrequent winking, and Moebius sign—the inability to converge properly on an approaching object near to the eye (this is owing to weakness of the internal rectus muscles of the eyes), and Kocher's sign—the immobility of the eyeball while the lid moves upward when following an object moving upward. These ocular signs are characteristic of exophthalmic goiter, and rarely occur in toxic adenoma.

The *basal metabolic rate* is characteristically increased in hyperthyroidism. This increase may be moderate ( $+15$  to  $+30$ ) or severe ( $+30$  to  $+70$ ). The study of the basal metabolic rate is probably the most important single diagnostic factor. Such a test is not only important in making the diagnosis, but it is important in estimating the results of treatment.

#### TREATMENT

The treatment of hyperthyroidism does not consist merely of treating the thyroid either by irradiation or operation, but the predisposing and exciting causes should be removed, and after active local treatment, the patient should be guided and guarded by competent medical advice such as the general practitioner can give.

Crile says, "In 3.3 per cent of our total cases, there is a recurrence of the hyperthyroidism after partial thyroidec-

be taken into consideration. In a former series of 533 cases reported by me, telangiectasis had occurred in 3 per cent of the cases, but all of these occurred in the earliest traced cases treated. There have been no such damaging effects in the recent series. Such damage depends upon the total amount of irradiation. While it may follow a single excessive dose of rays, it may occur without any erythema ever having been produced, provided there are many small doses given over a long period of time. I have not seen telangiectasis in any cases in which I had not given more than eight series, such as is described in my technic. I aim, therefore, to obtain results with from five to eight series. Even when present, with the exception of one case, telangiectasis has been only slight, and has not bothered the patients very much.

3. *Exacerbation of symptoms* may occur after the first treatment. This has rarely occurred in any of my cases. Such exacerbation has been especially emphasized by Borak, Pordes and Goerte. In my experience such an increase has been insignificant and no more than may occur from time to time independent of treatment. It must be borne in mind that patients will sometimes develop an increase in symptoms because of the new forms of treatment having been undertaken. If such an increase is feared, it may be well to decrease the dose in the first series, especially in the severe cases, and lessen the interval before the second series.

4. *Myxedema* has not occurred in any of my cases. Hypothyroidism occurred in four of the early series of cases reported, and in none in recent years. In only one of these four cases was it sufficiently severe to require the use of desiccated thyroid. Groover reported subsequent hypothyroidism in only 1.3 per cent of his cases. My low percentage of hypothyroidism after irradiation is in part due to the ability to reduce the excessive secretion gradually, and in part to the fact that the normal thyroid cells are resistant to irradiation. *Normal thyroid tissue and normal parathyroid tissue are resistant to irradiation and will not be affected by the amount of irradiation needed to control hyperthyroidism.* This has been proved not only by clinical observation but by the experimental work of Walters, Anson and Ivy, and by Bower

the adenoma (goiter) is the chief complaint of the patient, then I believe surgery will give the quickest and most satisfactory result. Sometimes brilliant results are obtained by irradiation with large goiters of this type. Hyperthyroidism is often overlooked or the diagnosis is delayed in patients past fifty (Bram). Bram mentions especially in this group of cases, tachycardia, palpitation, dyspnea, auricular fibrillation, asthenia or fatigability, and a coarse tremor, associated with arterial hypertension, as the most prominent symptoms.

#### Advantages of Irradiation

1. The fear of operation is eliminated and, therefore, the patient is more likely to come under treatment early and before cardiac damage has taken place.
2. If the patients are treated reasonably early, they are not interrupted in their occupation. When the disease is well advanced, or serious symptoms are present, they must, however, be put at rest.
3. There is no pain or shock and no great inconvenience, if the condition is treated reasonably early.
4. Patients with advanced disease or serious heart complications may be treated without shock, and, if radium is used, need not even be removed from their rooms or beds.
5. There is no risk of fatality from the treatment.
6. There is absence of scars or keloid formation.
7. The end-results are approximately equal to those obtained by surgery.

#### Objections to Irradiation Treatment

1. The danger of burns naturally comes into a patient's mind, because they occurred occasionally in the early years of irradiation therapy when the method was being developed, and when the dosage could not be accurately measured. Since such injured patients do not die, a few such accidents in the country become known far and wide; whereas, if a patient dies during an operation from an accident or any complication, the loss is accepted as one of the hazards of the procedure and may be ignored, or is soon forgotten.
2. *Telangiectasis and skin atrophy* are dangers which must

be taken into consideration. In a former series of 533 cases reported by me, telangiectasis had occurred in 3 per cent of the cases, but all of these occurred in the earliest traced cases treated. There have been no such damaging effects in the recent series. Such damage depends upon the total amount of irradiation. While it may follow a single excessive dose of rays, it may occur without any erythema ever having been produced, provided there are many small doses given over a long period of time. I have not seen telangiectasis in any cases in which I had not given more than eight series, such as is described in my technic. I aim, therefore, to obtain results with from five to eight series. Even when present, with the exception of one case, telangiectasis has been only slight, and has not bothered the patients very much.

3. *Exacerbation of symptoms* may occur after the first treatment. This has rarely occurred in any of my cases. Such exacerbation has been especially emphasized by Borak, Pordes and Goette. In my experience such an increase has been insignificant and no more than may occur from time to time independent of treatment. It must be borne in mind that patients will sometimes develop an increase in symptoms because of the new forms of treatment having been undertaken. If such an increase is feared, it may be well to decrease the dose in the first series, especially in the severe cases, and lessen the interval before the second series.

4. *Myxedema* has not occurred in any of my cases. Hypothyroidism occurred in four of the early series of cases reported, and in none in recent years. In only one of these four cases was it sufficiently severe to require the use of desiccated thyroid. Groover reported subsequent hypothyroidism in only 1.3 per cent of his cases. My low percentage of hypothyroidism after irradiation is in part due to the ability to reduce the excessive secretion gradually, and in part to the fact that the normal thyroid cells are resistant to irradiation. *Normal thyroid tissue and normal parathyroid tissue are resistant to irradiation and will not be affected by the amount of irradiation needed to control hyperthyroidism.* This has been proved not only by clinical observation but by the experimental work of Walters, Anson and Ivy, and by Bower



and Clark. Clinical proof of the absence of danger of damaging the thyroid cells or the parathyroids in the treatment of hyperthyroidism is shown by the fact that with the enormous amount of irradiation given in the treatment of cancer of the larynx, I have not observed any case of hypothyroidism or tetany, and I know of no such record in the medical literature. The fear of this, therefore, need not constitute objection to the treatment. *In hyperthyroidism the thyroid cells are quite radiosensitive.*

5. *Difficulty in subsequent surgical treatment*, if this should be necessary, has been adduced as an objection to irradiation. This objection need only be considered in a small percentage of cases (in only 7 per cent of my own cases was subsequent operation necessary, and in only one of these, an early case in the series, was any difficulty involved). It is now generally admitted that adhesions are found in as many cases which have not had previous irradiation as in cases which have been treated. Eiselsberg, who was first to consider adhesions as a postirradiation complication, now regards them as irrelevant.

6. *Slowness of response to irradiation* has been objected to, but with irradiation one usually gets some improvement at the end of a month and very definite improvement at the end of two months. If the surgeon uses two weeks for preparing his patient for operation, two weeks for recovery from the operation, and a month for convalescence, the time is two months; therefore, the difference in time is not so very great. At the end of these two months, however, one may generally expect a more complete relief of symptoms from surgery than from irradiation, because the surgeon removes the excess of glandular tissue at once, while with irradiation one reduces the hyperactivity and the hypertrophy or hyperplasia gradually. This is a slow and progressive effect. This slow response is not without its advantages, however, since the activity of the gland can be checked by frequent metabolic determinations and the final result controlled with greater nicety than when the hyperfunctioning gland is removed in one treatment. Therefore, if the patient is treated reasonably early, this slow recovery is not a serious objection. During this period of early treatment the internist should use all his

known methods of helping the patient (such methods to be discussed later).

7. The question of *permanent cardiac impairment* developing during the prolonged irradiation treatment must be considered, since the improvement from irradiation comes more slowly than from surgery, but this difference is not so great as would at first appear. Because of the fear of operation which leads to delay, and, therefore, damage to the heart, it is likely that if irradiation is considered the patient will be treated earlier, before serious damage to the heart has taken place. This advantage will make up for any delay in the result from irradiation.

Progress in cardiac impairment may also occur in cases treated surgically, as is indicated by the report made by Willius, in which he states: "At the time of initial examination at the Mayo Clinic, auricular fibrillation was found in 7 per cent of patients with exophthalmic goiter, and in 9 per cent of patients with hyperfunctioning adenoma. These percentages are doubled while the patient is under observation, that is, during the pre-operative, operative, and post-operative periods. Auricular fibrillation may occur as a permanent, intermittent, or paroxysmal disorder."

Holzknacht has stated that "not one case is found in the literature proving that the prolonged period of irradiation resulted in unnecessary damage to the heart."

8. *The danger of the development of carcinoma in toxic adenomas* has been advanced as a special argument in favor of operation in all toxic adenomas. No one can dispute that a considerable number of adenomas have been found to contain malignant tissue when removed and examined microscopically, but these early carcinomas are found in the non-toxic adenomas. Ewing says, "True tumors rarely develop in the Graves' thyroid." Cutler and Buschke state, "The hyperfunctioning thyroid rarely becomes the seat of cancer." In my experience, *in only one case out of a total of 501 cases of hyperthyroidism did carcinoma develop.*

This occurred in a female patient aged sixty-four. Her physician had recognized an adenoma in the middle lobe of the thyroid during three years. It was about 3 cm. in diameter and 2 cm. in thickness. The patient's pulse was irregular and the rate at rest was 88; after exercise it was 96. The basal metabolic rate, determined on two occasions, was  $\pm 20$  and

+15. The case was not clearly one of hyperthyroidism and I suggested operation, but both the patient and the attending physician wanted to avoid operation if possible. Therefore, we gave seven series of x-ray treatments between May 6, 1933, and April 10, 1934. Two basal metabolism tests done on May 8, 1934, showed +1 per cent and +6 per cent. The patient was symptom-free and seemed to be well. There was still present at that time an adenoma, approximately half its former size.

About October 1, 1935, the patient developed a sense of soreness in the neck, the pain extending up into the head, but the physician who referred the patient to me could find little wrong, yet he was unable to see below the vocal cords. The patient thought she was suffering from a cold. I examined her on October 21, 1935, at which time she was complaining of a sense of compression and of soreness upon swallowing. X-ray examination was made in a similar manner to that originally made on May 5, 1933. At that time (Oct. 21, 1935) I found that the anteroposterior diameter of the trachea was 15 mm., while at the examination on May 5, 1933, it was 11 mm. There did not, therefore, seem to be an increase in the compression. The heart shadow had decreased 1 cm. as compared with the examination on May 5, 1933.

On December 3, 1935, a surgeon operated upon her and found a blood clot. He also removed a specimen for microscopic examination but did not think that it was malignant. On December 13, 1935, the pathologist who examined the tissue reported carcinoma of the large cell type. The surgeon performed a tracheotomy, but a few days later the patient died. No one can tell, therefore, whether or not this patient would have lived longer if she had been operated upon, as I suggested when she first came to me, than she did by receiving irradiation treatment, which gave her freedom from symptoms for about two years. Had the diagnosis of carcinoma been made at the beginning she would, of course, have received more x-ray treatment.

There have surely been 5000 cases of goiter treated by irradiation and I cannot believe that if carcinoma had developed in any considerable number, the fact would have remained unreported. Therefore, it would seem that irradiation prevents the development of carcinoma, or, if carcinoma is present at the beginning of treatment, the x-ray evidently stops the growth of the carcinoma. Furthermore, it is recognized by everyone that for some reason carcinoma of the thyroid is unusually sensitive to irradiation.

For example, many years ago a woman patient was sent to me by a surgeon who had partially removed a carcinoma of the patient's thyroid. The surgeon told me definitely that he had not succeeded in removing all of the carcinoma. I treated the patient, and there was never any recurrence or development of this thyroid carcinoma during thirteen years. However, at the end of thirteen years she developed lung symptoms and we found extensive metastatic carcinoma scattered through the lungs. However, there was even then no evidence of any local carcinoma about the

TABLE 1\*  
CLASSIFICATION OF CASES

	1905-1933	1933-1937	1905-1937
Hyperthyroidism:			
Treated with x-rays.....	440 <sup>2</sup>	72 <sup>2</sup>	512
Treated with radium only.....	6	0	6
Nontoxic goiter treated with x-rays....	59	11	70
Carcinoma of thyroid..	28	0	28
	<hr/> 533	<hr/> 83 <sup>2</sup>	<hr/> 616
Cases not treated.....	165 <sup>4</sup>	39 <sup>5</sup>	204
	<hr/> 698	<hr/> 122	<hr/> 820

\* Including 40 cases treated at Women's Medical College.

<sup>2</sup> Including one case in which x-ray treatment was supplemented by radium therapy.<sup>4</sup> Including 11 cases in which treatment was abandoned by patient before completion, and three cases in which x-ray therapy was supplemented by operation<sup>5</sup> Nontoxic goiter.<sup>5</sup> Including 10 cases of hyperthyroidism and 29 cases of nontoxic goiter.

## X-RAY TREATMENT

1933-1937	Complete Series	X-ray Plus Subsequent Operation	Treatment Incomplete	Total Treated	Not Treated	Total
1. Hyperthyroidism:						
Exophthalmic goiter	31	0	1	32	1	33
Goiter without exophthalmos	10	2	4	16	5	21
No goiter or exophthalmos	11†	0	5	16	3	19
	<hr/> 52	<hr/> 2	<hr/> 10	<hr/> 64	<hr/> 9	<hr/> 73
Recurrent after operation	6	1	1	8	1	9
	<hr/> —	<hr/> —	<hr/> —	<hr/> —	<hr/> —	<hr/> —
Total hyperthyroid cases	58	3	11	72	10	82
	<hr/> 61	<hr/> —	<hr/> —	<hr/> —	<hr/> —	<hr/> —
2. Nontoxic goiter	9	2	0	11	29	40
	<hr/> 67	<hr/> 5	<hr/> 11	<hr/> 83	<hr/> 39	<hr/> 122

\* These statistics have been prepared from a review of many cases by my associate, D. A. Sampson, M. D.

† In 1905-1933, there were 45 cases.

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to 40 per cent of an erythema dose (210–280 r) is given through each of these four portals. I usually use the low voltage rays (130 kv.), with 5 ma. and eleven minutes' ex-

TABLE 2  
RESULTS OF X-RAY TREATMENT, 1933–1937\*

	No. of Cases	Cured	Markedly Improved	Not Improved
1. Hyperthyroidism:				
Exophthalmic .....	31	18 (58%)	13 (42%)	0
Goiter without exophthalmos.....	12	7 (58%)	2 (17%)	3 <sup>1</sup> (25%)
No goiter or exophthalmos.....	11	9 (82%)	2 (18%)	0
Recurrent after operation.....	7	4 <sup>2</sup> (57%)	3 <sup>3</sup> (43%)	0
	61	38 (62%)	20 (33%)	3 (5%)
2. Nontoxic goiter.....	11	6 (56%)	3 <sup>4</sup> (27%)	2 <sup>5</sup> (18%)
	72	44	23	5

<sup>1</sup> Two patients subsequently had operation.

<sup>2</sup> One case of nontoxic goiter included—operation 24 years previously.

<sup>3</sup> One patient subsequently had operation.

<sup>4</sup> One patient subsequently had operation.

<sup>5</sup> One patient subsequently had operation.

COMPARISON OF RESULTS IN YEARS 1905–1933 AND 1933–1937

	No. of Cases	Cured	Markedly Improved	Not Improved
1905–1933 .....	440	252 (57%)	135 (31%)	53 (12%)
1933–1937.....	61	38 (62%)	20 (33%)	3 (5%)
Total 1905–1937.....	501	290 (58%)	155 (31%)	56 (11%)
Total (cured or markedly improved).....		445 (89%)		

\* These statistics have been prepared from a review of my cases by my associate, D. A. Sampson, M. D.

posure at a distance of 30 cm., and use a combination filter of copper and aluminum equivalent to 6 mm. of aluminum.

Usually this treatment is given on one day so as to save the patient the trouble of coming for treatment repeatedly. Under certain circumstances, it may be advisable to divide these treatments over four different days or over two days.

thyroid or around the neck, or in any of the areas which had received treatment, even though it was known to be present when I began treatment. This proves that I did control the carcinoma completely within the areas where the radiation was applied.

Other cases in my experience and those of other radiologists have also given convincing proof of the radiosensitivity of carcinoma of the thyroid. Therefore, I believe that we need not let this fear influence us in the selection of treatment. The nomenclature frequently used by the internists and surgeons is "economic restitution" or "rehabilitation." In my series of cases, it can be seen that an 89 per cent "economic restitution" or "rehabilitation" was obtained.

*Hyperthyroidism without Palpable Glandular Enlargement.*—The diagnosis in this group of cases is much more difficult, and it is quite natural that a much larger percentage of such cases should come to the radiologist than to the surgeon. In my group there were fifty-nine of these cases: economic restitution occurred in forty-eight; the treatment failed in seven, and four patients could not be traced.

### Technic of Roentgen Therapy

I routinely employ roentgen rays, using 130 kv., 5 ma., and 30 cm. distance, with the equivalent of 6 mm. of aluminum filtration. The cervical region is divided into four fields, each approximately 5 by 10 cm., the outline of each field being that of a truncated cone. Two of these fields are anterior, and two posterolateral. The anterior field, a truncated cone in shape, is arranged so that the inner border is near the median line. I usually try to allow 1 cm. between the two anterior fields centrally, and the upper limit comes just to the upper border of the thyroid, which usually protects the arytenoids and the cords. The lower border extends below the clavicle and includes the thymic area. The larynx is protected with lead. The rays are directed medially and downward so that a cross-firing effect is obtained in the thyroid and thymus region. The two posterior fields meet the anterior field to within about 1 cm., and the rays are directed downward and inward through the region of the cervical sympathetic ganglia toward the thyroid and thymus. Thirty

to 40 per cent of an erythema dose (210–280 r) is given through each of these four portals. I usually use the low voltage rays (130 kv.), with 5 ma. and eleven minutes' ex-

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posure at a distance of 30 cm., and use a combination filter of copper and aluminum equivalent to 6 mm. of aluminum.

Usually this treatment is given on one day so as to save the patient the trouble of coming for treatment repeatedly. Under certain circumstances, it may be advisable to divide these treatments over four different days or over two days.



The series is repeated in three weeks, then in four weeks, and after that the interval is increased according to the improvements obtained. These several small doses will often be sufficient to show a definite decrease in the size of the goiter. In adenomas, localized doses are usually employed with cross-firing of the adenoma through two portals.

In the severer cases, it is better to begin with smaller doses and perhaps repeat in a shorter time. This dose may be increased subsequently and the interval also increased. More than six series are rarely necessary, and I usually count on giving the patient from five to eight such series. I am reluctant to give more than eight such series. If a patient is not definitely improved after from three to five series and after a lapse of two or three months from beginning of treatment, other measures should be employed.

#### Treatment of Hyperthyroidism by Roentgen Irradiation of the Pituitary Gland (Borak)

Pollitzer, Holzknecht and Borak believe that there exists hypophyseal Basedow's disease. Jüggenberg had the impression that x-ray treatment of the thyroid in aged women with Basedow's disease gave poorer results than in younger women. She reported the detailed histories of seven women in whom the typical symptoms of Basedow's disease had come on after the climacteric, treated in vain with medical means and by irradiation of the thyroid, who were markedly benefited by irradiation of the pituitary. Borak reported ten similar cases, in his own experience, treated between 1925 and 1929. He referred to the biological foundation for the treatment of the pituitary in experiments of Loeb in America, and Aron in France, working independently of each other. These authorities produced typical Basedow's disease by the injection of hypophyseal extracts, and the intensity of the symptoms varied with intensity or the number of the injections. The injection of milk or tissue extract did not produce these results.

Borak says, "In the course of the past twenty-five years, we have become completely convinced of the absolute safety of irradiating the pituitary because the brain surrounding the gland has been demonstrated, both clinically and experimentally, to be tissue especially capable of

tolerating with impunity even the strongest doses likely to be used in therapeutic procedures."

Borak has treated the pituitary in thirty-six cases of hyperthyroidism. Of the thirty-six cases, 77 per cent showed favorable results. Of sixteen cases treated primarily by irradiation of the pituitary, good results were obtained in ten (62.5 per cent). Of these ten cases, nine were women in whom hyperthyroidism came on after the onset of the menopause. He recommends treatment of the pituitary in all those women past the menopause, and treatment of the thyroid in those preceding the menopause. He states, "Improvement grows in both types of treatment from the general to the particular, from the subjective symptoms to the objective symptoms. The nervous symptoms, the irritability, the fatigability, sleeplessness, headache improve first. Then the body weight begins to increase and the basal metabolic rate to decrease. Then there begins an improvement in the classic triad, so that the face of the thyroidism is the last to clear up. The tachycardia, the goiter, and the exophthalmos disappear slowly and in some cases there is complete return to normal."

*Technic of Pituitary Treatment.*—Borak further says, "We treat the thyroid through an anterior and two lateral fields at two-day intervals. In the same way the pituitary is treated through a frontal and two temporal fields. The dose on the skin at each treatment, as it is in the case of the thyroid, is 200 r. Because of the fact that the thyroid is quite superficial and the pituitary is located at a depth of 7 cm., on the average, and so the effective dose is only about 40 per cent of that effective in the skin, the three fields are treated for a second time after eight days. The other treatment factors are 0.5 mm. zinc filter, 30 cm. distance, 170 kilovolts.

"If the basal metabolic rate or the pulse deviate greatly from normal at the end of eight weeks, we repeat the radiation series. We have given a third series only in case of recurrence.

"Aside from headache, which occurs now and then on the day of treatment, we have never seen any upset from irradiation of the pituitary. This agrees perfectly with what has happened in the thousands of pituitary treatments which I have given for various reasons to hundreds of patients during the last ten years. This roentgenologic technic is perfectly safe and without any danger whatever."

### Iodine and Roentgen Therapy in Hyperthyroidism

I am convinced that it is inadvisable to use iodine in conjunction with roentgen therapy. As has been shown in the previous discussion, *the roentgen rays have an excellent effect on the thyroid cells when they are in an excited stage*, but the rays have very little effect on the thyroid when the cells are not stimulated or in an excited condition. Therefore, if we quiet this hyperactivity temporarily by the iodine, we fail to get the satisfactory effects from the irradiation which are more permanent, and it is well known the iodine loses its effect. It is well known that iodine does give good results in

exophthalmic goiter, also in about half of the toxic adenomas, but these effects are lost after a time, and it is not considered good technic to continue over long periods. I prefer to treat a patient who has not even had iodine treatment, because it seems to me that I get definitely better results. The Mayos stated, "At the Mayo Clinic, iodine is not administered except for special purposes to a patient who had adenomatous goiter *without* hyperthyroidism. However, since 1923, it has been freely but not routinely administered to patients who had adenomatous goiter *with* hyperthyroidism and no harm had been seen with such use *within the week or two before operation* had been performed."

With regard to the effects of iodine in adenomatous goiter, I cannot do better than to quote from Jackson and Freeman, who write in their summary:

"1. There may be produced iodine-fast cases of exophthalmic goiter.

"2. Iodine not only does no good but is definitely contra-indicated in non-toxic adenomas of the thyroid.

"3. There is danger in administering iodine in cases of adenomatous goiter, of producing iodine hyperthyroidism.

"4. Adenomatous goiter does not become toxic before the patient has reached the age of 30 unless the toxicity is brought on by the injudicious use of iodine.

"5. We have shown that iodine may and does produce thyrotoxicosis in adenomatous goiter, as opposed to the contention of Means and Lerman.

"6. The effect of aqueous solution of iodine in toxic adenoma is not constant or specific and is not the same as that produced in exophthalmic goiter.

"7. Approximately 62 per cent of all cases of toxic adenoma are benefited by iodine or are not affected, while 38 per cent are made worse.

"8. In a series of cases of toxic adenomas, toxic symptoms and the basal metabolic rate were aggravated by aqueous solution of iodine.

"9. Owing to its variability of action, we believe that iodine should be given as a routine in all cases of toxic adenoma *before and after operation*, because two-thirds of the cases will be improved, and the harmful effects on the third is negligible over a *short time*."

It will be seen that iodine cannot be given indiscriminately to patients suffering from toxic adenoma. In a few cases in which the attending physician believed that the iodine was absolutely necessary, I requested that the iodine be discontinued for a period lasting from a few days to a week before the irradiation was to be given. It probably will not interfere if given after the treatment or between treatments, though I prefer to work independently; then I can judge my results.

## General Care and Observations

A careful record of the patient's pulse, weight, general health, and the condition of the skin is made at each visit, and frequent metabolic determinations are made. Foci of infection are removed. Chest examinations are made routinely on each patient before treatment is begun. I recommend administration of quinine hydrobromide, 5 grains three times a day, unless ringing in the ears occurs (Bram). Dodd's lotion is prescribed for application to the neck to avoid skin damage. The patient is cautioned against sunburning the neck or applying irritating salves or lotions. *Rest, so far as practicable, is advised, the patient being told never to stand when he can sit, and never to sit when he can lie down.* A high caloric diet of easily digested food is recommended. Bread and butter, cereals, dairy products, practically all varieties of fruits and vegetables constitute the major dietary ingredients and should be taken in maximal amount. Until he or she regains weight, the average patient requires practically twice the amount of food taken during health. *Tea, coffee, condiments, spices, and all alcoholic stimulants should be strictly forbidden. Tobacco should be stopped.* Diet has been especially emphasized by Bram.

Means, Hertz and Lerman have recently not only emphasized the importance of the uncontrolled factors in Graves' disease, but have called attention to the fact that *not only does hyperthyroidism cause a loss of weight but a loss of weight may cause hyperthyroidism, and have made a report of thirty-five such cases* (the hyperthyroidism developed in fourteen of the thirty-five cases following weight-reduction cures). Aub. Bauer, Heath and Ropes have also called attention to the marked excretion of calcium and phosphorus in connection with thyroid disease and parathyroid disease. They call attention to the fact that in hyperthyroidism the calcium loss is great but the serum calcium is not increased. This loss of calcium not only depends upon the disease but also to a certain extent upon the intake of calcium. On that account I am giving hyperthyroid patients, in addition, an increased amount of calcium together with cod liver oil in some form. This seems to be logical and certainly can do no

exophthalmic goiter, also in about half of the toxic adenomas, but these effects are lost after a time, and it is not considered good technic to continue over long periods. I prefer to treat a patient who has not even had iodine treatment, because it seems to me that I get definitely better results. The Mayos stated, "At the Mayo Clinic, iodine is not administered except for special purposes to a patient who had adenomatous goiter *without* hyperthyroidism. However, since 1923, it has been freely but not routinely administered to patients who had adenomatous goiter *with* hyperthyroidism and no harm had been seen with such use *within the week or two before operation* had been performed."

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It will be seen that iodine cannot be given indiscriminately to patients suffering from toxic adenoma. In a few cases in which the attending physician believed that the iodine was absolutely necessary, I requested that the iodine be discontinued for a period lasting from a few days to a week before the irradiation was to be given. It probably will not interfere if given after the treatment or between treatments, though I prefer to work independently; then I can judge my results.

## General Care and Observations

A careful record of the patient's pulse, weight, general health, and the condition of the skin is made at each visit, and frequent metabolic determinations are made. Foci of infection are removed. Chest examinations are made routinely on each patient before treatment is begun. I recommend administration of quinine hydrobromide, 5 grains three times a day, unless ringing in the ears occurs (Bram). Dodd's lotion is prescribed for application to the neck to avoid skin damage. The patient is cautioned against sunburning the neck or applying irritating salves or lotions. *Rest, so far as practicable, is advised, the patient being told never to stand when he can sit, and never to sit when he can lie down.* A high caloric diet of easily digested food is recommended. Bread and butter, cereals, dairy products, practically all varieties of fruits and vegetables constitute the major dietary ingredients and should be taken in maximal amount. Until he or she regains weight, the average patient requires practically twice the amount of food taken during health. *Tea, coffee, condiments, spices, and all alcoholic stimulants should be strictly forbidden. Tobacco should be stopped.* Diet has been especially emphasized by Bram.

Means, Hertz and Lerman have recently not only emphasized the importance of the uncontrolled factors in Graves' disease, but have called attention to the fact that *not only does hyperthyroidism cause a loss of weight but a loss of weight may cause hyperthyroidism, and have made a report of thirty-five such cases* (the hyperthyroidism developed in fourteen of the thirty-five cases following weight-reduction cures). Aub. Bauer, Heath and Ropes have also called attention to the marked excretion of calcium and phosphorus in connection with thyroid disease and parathyroid disease. They call attention to the fact that in hyperthyroidism the calcium loss is great but the serum calcium is not increased. This loss of calcium not only depends upon the disease but also to a certain extent upon the intake of calcium. On that account I am giving hyperthyroid patients, in addition, an increased amount of calcium together with cod liver oil in some form. This seems to be logical and certainly can do no

exophthalmic goiter, also in about half of the toxic adenomas, but these effects are lost after a time, and it is not considered good technic to continue over long periods. I prefer to treat a patient who has not even had iodine treatment, because it seems to me that I get definitely better results. The Mayos stated, "At the Mayo Clinic, iodine is not administered except for special purposes to a patient who had adenomatous goiter *without* hyperthyroidism. However, since 1923, it has been freely but not routinely administered to patients who had adenomatous goiter *with* hyperthyroidism and no harm had been seen with such use *within the week or two before operation* had been performed."

With regard to the effects of iodine in adenomatous goiter, I cannot do better than to quote from Jackson and Freeman, who write in their summary:

- "1. There may be produced iodine-fast cases of exophthalmic goiter.
- "2. Iodine not only does no good but is definitely contra-indicated in non-toxic adenomas of the thyroid.
- "3. There is danger in administering iodine in cases of adenomatous goiter, of producing iodine hyperthyroidism.
- "4. Adenomatous goiter does not become toxic before the patient has reached the age of 30 unless the toxicity is brought on by the injudicious use of iodine.
- "5. We have shown that iodine may and does produce thyrotoxicosis in adenomatous goiter, as opposed to the contention of Means and Lerman.
- "6. The effect of aqueous solution of iodine in toxic adenoma is not constant or specific and is not the same as that produced in exophthalmic goiter.
- "7. Approximately 62 per cent of all cases of toxic adenoma are benefited by iodine or are not affected, while 38 per cent are made worse.
- "8. In a series of cases of toxic adenomas, toxic symptoms and the basal metabolic rate were aggravated by aqueous solution of iodine.
- "9. Owing to its variability of action, we believe that iodine should be given as a routine in all cases of toxic adenoma *before and after operation*, because two-thirds of the cases will be improved, and the harmful effects on the third is negligible over a *short time*."

It will be seen that iodine cannot be given indiscriminately to patients suffering from toxic adenoma. In a few cases in which the attending physician believed that the iodine was absolutely necessary, I requested that the iodine be discontinued for a period lasting from a few days to a week *before* the irradiation was to be given. It probably will not interfere if given after the treatment or between treatments, though I prefer to work independently; then I can judge my results.

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harm. Aub, Bauer, Heath and Ropes also call attention to the specific role in thyrotoxicosis that may be played by a storage of vitamin B. Schmidt, Walsh and Chesky recommend the administration of liver extract parenterally. It seems, therefore, important that not only should the patient be given a high caloric diet, but should also have a high vitamin diet. For the high caloric intake the chief dependence should be placed upon carbohydrates. Excessive protein is undesirable because, through its specific dynamic action, protein raises metabolism. Carbohydrates, on the other hand, in large amounts are insurance against depletion of the glycogen stores of the liver and thus safeguard that organ.

#### SUMMARY AND CONCLUSIONS

1. Irradiation with either roentgen ray or radium may be accepted as a useful method of treatment of hyperthyroidism, since the end-results are approximately equal to those obtained by surgery.

2. The fear of operation or delays preceding operation are likely to lead to cardiac enlargement. This delay can be eliminated by the use of irradiation therapy.

3. Irradiation therapy does not involve shock or great inconvenience.

4. Associated medical care and general directions for conservation of energy are essential.

5. Irradiation is probably of value in the prevention of the development of carcinoma.

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## DIAGNOSIS AND TREATMENT OF THYMIC HYPERPLASIA\*

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AN infant, aged two months, male, was admitted to the service of Dr. John P. Scott, Children's Hospital, October 7, 1940. After correlation of the history with the physical examination and laboratory findings, a diagnosis of amyotonia congenita was made.

Muscular atonia was marked although the musculature of the patient appeared to be normal. A routine roentgenological examination of the chest revealed a dense shadow, triangular in shape, extending upward and outward from the right hilum into the right upper lobe merging with the shadow of the mediastinum (Fig. 224). In the lateral view (Fig. 225), the anterior portion of the chest corresponding to the right upper lobe was dense. On fluoroscopic examination the dense area in the upper portion of the right side of the chest showed no pulsation, either transmitted or expansile. It was thought that this dense area was due either to an enlarged thymus or to partial atelectasis of the right upper lobe or possibly to a combination of both.

The patient died on November 15, 1940, and an autopsy was performed (Fig. 226). The thorax when opened showed no excess of fluid and no adhesions in either the pleural or pericardial sacs. The thymus was short and thick and weighed 22 gm. and measured 5 by 7 by 2 cm. Its parenchyma had the usual, pale, fleshy appearance. The posterior half of each lung was purplish grey, moist and somewhat atelectatic. On correlation with the roentgenogram of the chest, it was determined definitely that the dense shadow was cast by the thymus and only in a small part, if at all, by the atelectatic upper lobe of the right lung.

Two weeks before death, an x-ray treatment was given over the anterior chest, the factors being 130 kv., 3 mm. aluminum filter, 70 r measured in air. There was no perceptible effect on the width of the thymic shadow on subsequent roentgenological examination.

This case serves well as an introduction to a discussion of the diagnosis and treatment of thymic hyperplasia, since it immediately brings to mind several questions: (1) What is

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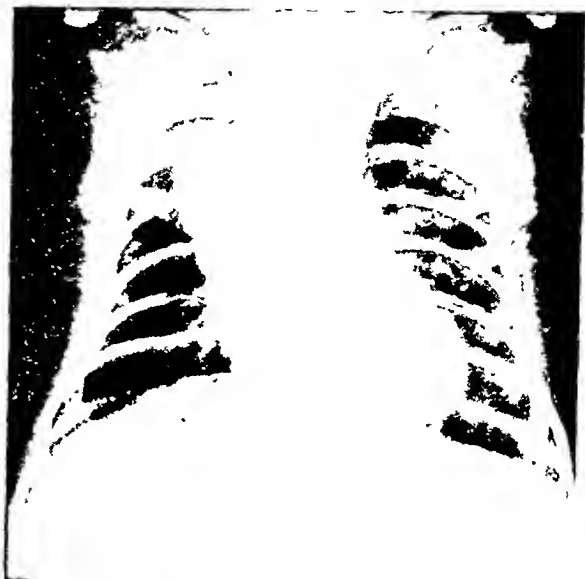


Fig. 224.—Anteroposterior view of the chest showing the dense shadow cast by the enlarged thymus on the right side of the mediastinum.



Fig. 225.—Lateral view showing no demonstrable pressure on the trachea.

the normal size of the thymus? (2) Does thymic enlargement cause symptoms? (3) What are the roentgenological criteria for the diagnosis of thymic hyperplasia?



Fig. 226.—The enlarged thymus at autopsy is shown projecting downward over the base of the heart and overlapping the right lung.

#### THE NORMAL SIZE AND WEIGHT OF THE THYMUS

Before any consideration can be given to the diagnosis of thymic enlargement, the size and weight of the normal thymus should be determined. As is the case in all phases of diagnosis and treatment of thymic hyperplasia, the determination of the normal size and weight has been a controversial issue. The weight of the thymus in this infant at the age of two months was 20 gm., well above the weight for this age given in the table of ages and weights quoted by Mitchell. On consulting the literature, marked variations in the size and weight considered to be normal are found due to the fact that many of the older observations were based on

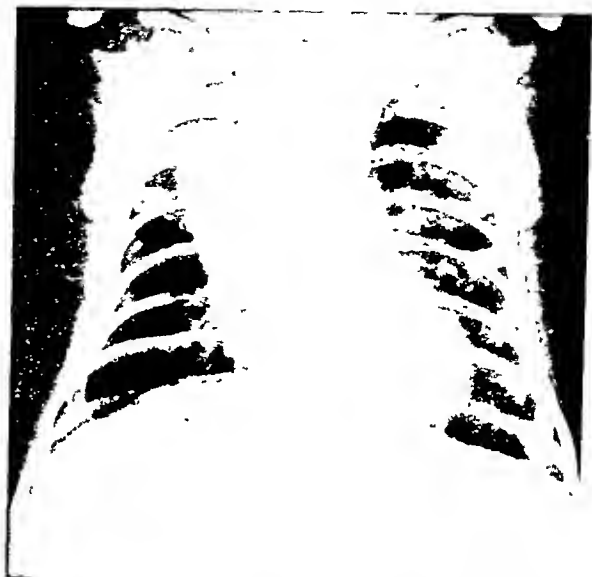


Fig. 224.—Anteroposterior view of the chest showing the dense shadow cast by the enlarged thymus on the right side of the mediastinum.



Fig. 225.—Lateral view showing no demonstrable pressure on the trachea.

the trachea is responsible. Much controversy is found in the literature over the question whether the thymus, a relatively soft organ, can cause pressure on the trachea sufficient to produce symptoms. In the patient under consideration, the thymus was undoubtedly enlarged but at no time did the infant show any symptoms which could be attributed to the enlarged thymus. Noback in his anatomical studies showed that the lobulated shape of the thymus is determined early in fetal life. The bilobed type frequently predominates. It is located in a cervicothoracic position. It is broad in outline, extends laterally to the anterior axillary line in most cases and is practically never overlapped by the fetal lungs. This broad type of thymus is the fetal type since he showed it was typically found in full term stillborn infants.

In regard to the question of pressure on the trachea, Noback's findings are interesting. The thymus of infants in whom respiration has been practically or wholly established is usually more thoracic in location than the fetal type. It bears the impress of the organs with which it comes in contact. The right lung extended over its anterior surface in every one of his cases while the left lung extended over the anterior surface in four out of five of his cases. The transition from the broad or fetal type to the elongated or molded type of thymus found in the infant who has breathed, is accomplished during the time in which respiration is completely established. The expansion of the lung changes the position in relation to the thoracic contents and, along with the other organs of the thorax, the thymus is markedly affected. It is compressed both laterally and anteroposteriorly with the resulting elongation and extension over the right ventricle. Noback believes that in the neonatal period the degree of expansion of the lungs is a more potent factor in determining the lateral extent of the thymus than is the actual size of the organ during this period. The thymus lying in the usually described normal area may exert marked pressure on the structures posterior to it. This may be due either to a very large thymus or to a narrow superior thoracic aperture, which will not allow the thymus to protrude into the cervical region as it is compressed by the expanding lung.



autopsies of patients who had suffered varied illnesses. They were not based on the autopsies of patients who died suddenly from trauma or other causes.

The weight of the thymus is dependent upon the general nutritional state of the body. Boyd has shown that, in children dying of very rapid fulminating infections within twenty-four hours of the onset of their illness, the weight of the thymus is still within the normal zone of variation in size. In cases of death from one day to one week after the onset, there is found a definite reduction in the size of the thymus. Therefore, Boyd states that what was considered formerly the normal weight of the thymus actually represented a pathological reduction in size.

It is now generally agreed that a temporary reduction in the weight of the thymus occurs during the first two weeks of life. This is soon regained and it increases in size until the age of puberty. However, in relation to body weight it actually decreases from the time of birth, rather slowly in the first year, rapidly throughout childhood and more rapidly after puberty. The figures given by Mitchell range from a weight of 10 to 14 gm. at birth, 20 gm. at six months, 22 gm. at five years up to 35 gm. at fifteen years. These can only be regarded as approximate weights.

#### SYMPTOMS OF THYMIC HYPERPLASIA

Among the symptoms attributed to thymic hyperplasia, chronic or paroxysmal *stridor* and *cyanosis* are usually mentioned. To these should be added *wheezing respiration*. The stridor is described by some as inspiratory in nature while others claim it occurs during expiration. A peculiar crowing noise is also mentioned by many writers. Difficulty in swallowing, choking attacks and, in older children, a brassy cough have been placed in the category of thymic symptoms. Attacks of "holding the breath" are regarded as significant of thymic involvement but there is little if any evidence to support this contention.

#### Compression of Trachea by Enlarged Thymus

In explanation of the cause of these symptoms the theory is usually advanced that pressure of the enlarged thymus on

A very complete study of the question whether such an entity existed was made by the British Research Council in which it was found that there was no concomitant general hyperplasia of lymphoid structures in cases of abnormally large thymus. Boyd and others now claim that the condition described by Paltauf represents only the normal thymus and lymphoid tissue of a well-nourished young subject.

In the report of the British Research Council and in those of other authors, no constant enlargement of the thymus in cases of sudden death from unexplained causes was found. Sudden death has been claimed by many to be due to the condition, such as death during general anesthesia, during operations under local anesthesia, during hypodermic injections, or during the administration of diphtheria antitoxin; death from chilling of body surfaces or extraction of teeth; sudden death after fracture or psychic shock or in the instances when a child is found dead in bed, death having occurred apparently in sudden manner during sleep. In a panel discussion at a meeting of the American Academy of Pediatrics, 1938, most of the members of the panel agreed that it would be well to discard the term "status thymicolymphaticus," and that if the thymus is in any way related to sudden death, it could only be in a secondary capacity; that roentgen therapy or extirpation of the gland would not have any effect in preventing sudden death.

#### THE ROENTGENOLOGIC DIAGNOSIS OF THYMIC HYPERPLASIA

In the anteroposterior roentgenogram of the chest the normal thymic shadow is merged with that of the base of the heart, the great vessels and the structures forming the mediastinal shadow. In descriptions of this region by most authors it is stated that when the thymus is enlarged its shadow extends upward above the base of the heart causing an increased width of the mediastinal shadow. This is sometimes more marked on the left side than on the right. It is sometimes even broader than the total transverse diameter of the heart. It increases in width, supposedly, when the child cries and also during expiration. It is supposed to ascend on

In support of the theory of thymic pressure, Pancoast quoted Jackson who observed, by means of the bronchoscope, tracheal compression caused by the thymus. This occurred in patients who had symptoms such as wheezing, dyspnea and impending asphyxia. Pancoast believed that an abnormal blocking or narrowing of the trachea, shown in the lateral roentgenograms of the chest in the inspiratory phase, indicated compression by the enlarged thymus. This narrowing is located at the thoracic inlet where the trachea passes over the apex of the thymus. He regarded lateral deviation of the trachea in the roentgenogram exposed with the patient lying face down on the film, as additional evidence of compression. He thought it likely that not only could there be compression of the trachea but that pressure on the superior laryngeal nerve could occur and produce symptoms of a laryngeal nature.

In reviews of the literature by various authors the opinion is now prevalent that while compression of the trachea or obstructive symptoms due to an enlarged thymus can occur, such occurrences are extremely rare. Other causes for compression of the trachea must be excluded before such a diagnosis can be made.

#### STATUS THYMICOLYMPHATICUS

No discussion of thymic hyperplasia is complete without mention of status thymicolymphaticus. The term was given by Paltauf to a pathological condition in which thymic hyperplasia was found accompanied by, or as a part of, a general involvement of the lymphatic system. Mitchell lists the following as manifestations of the supposed entity as claimed by various authors: enlargement of the spleen, thymus and lymphatic tissues in general including those of the nasopharynx and the follicles at the base of the tongue; arrested development of the chromaffin system, a familial predisposition to the condition; a preponderance in males; flabbiness of muscles and relaxation of ligaments; paleness, lack of strength and resistance to infection; a tendency to eczema and allergic conditions; increase of lymphocytes in the blood and the liability to sudden death.

enlarged thymus; the borders are more convex and the shadow is characteristically wide at the root of the lung, gradually narrowing to the outer boundary.

### ROENTGEN THERAPY OF THE THYMUS

The controversy raging in regard to the question whether thymic enlargement is responsible for the symptoms which have been enumerated has undoubtedly resulted in the past eight or more years in a great decrease in the number of infants and children treated for this condition. It has been the experience of many careful observers to note an apparent cause and effect between roentgen irradiation of the thymus and the relief of obstructive symptoms. This has been reported in a sufficient number of cases to warrant irradiation when no other cause for the symptoms can be found. In fact, even if the roentgen examination fails to confirm the presence of an enlarged thymus, treatment may be given to relieve symptoms which warrant a clinical diagnosis. Thus, *clinical diagnosis*, other causes of obstructive symptoms having been eliminated, is the deciding factor in administering roentgen therapy.

There is no good reason for the routine radiologic treatment of newborn infants or of children of any age simply because the roentgenogram suggests the presence of thymic hyperplasia. The practice which was the routine in many hospitals, some years ago, to examine all infants born on the maternity service has been discontinued in almost all instances. Likewise the routine examination of all children to be given an anesthetic has been discontinued. About ten years ago, at the Children's Hospital, all patients who were listed for tonsillectomy were examined roentgenologically for possible thymic enlargement. In none were shadows found sufficient to indicate thymic enlargement. If the patient who is to be given a general anesthetic has a history of a previous diagnosis of an enlarged thymus in infancy, a roentgenological examination should be made. A treatment may be given if evidence of hyperplasia is found but it is now generally agreed that this cannot be regarded as a prophylactic measure or an insurance against sudden death.

expiration and descend on inspiration but this at times is very difficult to demonstrate. Its shape may be varied, one of the most usually described being that of the inverted keystone. Sometimes it is globular or it may have a bulging, lobulated appearance, crescentic in outline on either side of the mediastinum.

Harrison states that it is possible for the thymus to enlarge mainly in the anteroposterior plane in much the same manner as an enlargement of the thyroid gland may be limited to a definite lobule. In such cases its situation in front of the trachea and the fixation anteriorly by the rigid sternum force the trachea backward. The effect of the enlargement can be readily recognized by the sharp, backward curve which the trachea takes at the thoracic inlet. If the pressure, as shown in the anteroposterior plane, is still more marked the trachea becomes flattened from before backward and may be even ribbon-like in appearance.

Pancoast emphasized the necessity for exposure of roentgenograms in the erect position to prevent distortion. Exposures must be made also in both expiration and inspiration. He believed that little attention need be paid to the width of the shadow in the anteroposterior views, the diagnosis being made entirely on the evidence of compression in the lateral projections exposed during the inspiratory phase, and on the lateral displacement of the trachea in the anteroposterior exposures. In this way he attempted to gauge the upward push of the thymus into the thoracic inlet.

In the *differential diagnosis* it is necessary to rule out a congenital cardiac lesion with increased width of the heart shadow on both sides of the mediastinum. Fluoroscopy is of assistance in making this differentiation. Partial atelectasis of the upper lobes of both lungs may be mistaken for thymic enlargement. Thymoma and lymphosarcoma produce wide mediastinal shadows but the accompanying clinical picture should aid in the differential diagnosis. Enlarged tracheobronchial and mediastinal lymph nodes, either of tuberculous or nontuberculous origin, also cause enlargement of the mediastinal shadow. Remer and Belden state that the shadow cast by tuberculous nodes is usually denser than that of an

have been reported must be mentioned. Some of these are cretinism, tetany resulting from disturbed calcium metabolism, arrest of growth and a condition described as thymic idiocy resembling the mongolian type. However, the studies of Barnes and Polk and Rose confirm the general opinion that no ill effects, no retardation of physical growth or mental development which could be attributed to fairly heavy irradiation over the thymic region occur. The dosage employed in the cases studied by Barnes was somewhat high as compared with our present technic but, in spite of this, no damage resulted. Cretinism and tetany as late results might be attributed to overdosage with inclusion of the thyroid and parathyroids within the field irradiated. It is generally conceded that very heavy dosage would be necessary to produce such damage to these glands.

Gershon-Cohen and Shay destroyed the thymus gland by roentgen irradiation in rats and showed a close relationship between the function of the thymus and proper development of the testes. They demonstrated, too, changes in the gonads and pituitary gland of rats following destruction of the thymus by irradiation. The dosages employed were much greater than analogous doses used in the treatment of children with thymic hyperplasia.

The question may be asked, Why was irradiation employed in the patient under consideration? It was felt that if the enlarged mediastinal shadow was due to an enlarged thymus some benefit might be obtained by treatment and, without doubt, no harm to the patient would ensue from the dosage used. No reports of enlargement of the thymus in amyotonia congenita have been found in the literature. In passing, it is interesting to note that thymic hyperplasia has been observed in a fair percentage of cases of myasthenia gravis. In some patients with this condition, thymomas were found. Good results have been obtained following extirpation of the gland and by the use of roentgen therapy. The significance of this finding is not known and adds another interesting phase to the "thymic question."

If roentgen therapy is decided upon in any case, *the dosage must be comparatively light*. A range of dosage from 50 to

Boyd has drawn attention to the fact that children dying of acute respiratory symptoms within the first few days of the illness show thickening of the mucous membranes of the trachea and bronchi. Without doubt many of these children also have enlarged mediastinal nodes which drain the infected areas. It is likely that enlarged nodes which cast a shadow similar to that of an enlarged thymus have at times been treated by irradiation, and improvement following the treatment has been due to the effect of the irradiation upon the infected and enlarged nodes and not to a decrease in the size of the thymus. Boyd also believes that the thymus is not a particularly vascular organ. If there is congestion of the mediastinum it is due to dilatation of the innominate vein and not to a congested and enlarged thymus. The largest vein coming from the thymus is the one that goes directly into the innominate vein. It usually measures about 2 mm. in diameter and fits closely around the innominate vein so that congestion of the latter may result. Noback, however, described a case in which, at autopsy, actual pressure by an enlarged thymus on the innominate vein was found.

If favorable results from irradiation are obtained both clinically and roentgenologically by reduction in the size of the thymic shadow, the clinical improvement is attributed by many writers to reduction in the size of the gland. Hammer has shown that this is effected chiefly by a decrease in the lymphocytic elements. Disintegration of these begins after a few hours and they are taken up phagocytically by the reticulum cells. If exposure has not been too great, a restoration of the lymphocytes may later occur. The reduction in the size of the gland may not take place for a number of days but the symptoms are nevertheless promptly relieved.

Some have claimed that the real cause of symptoms is not of thymic origin but that spasm of the larynx, cardiac failure or sudden fall in blood pressure are caused by overactivity of the vagus resulting from involution of the suprarenals, deficiency of the chromaffin system and inadequacy of the sympathetic system. Aldrich quotes Peterson who suggested that the action of the rays on the lymphatic structures causes a nonspecific reaction which in turn causes an effect antagonistic to the vagus. Cases have been reported in which roentgen treatment of an enlarged thymus has apparently caused improvement in symptoms referable to pylorospasm in infants. In explanation of this, the theory has been advanced that pylorospasm and thymic enlargement are dependent upon vagotonia resulting from insufficient production of epinephrine. If it can be proved that the theory of vagotonia as a cause of symptoms is correct and that irradiation has an antagonism to vagotonia, then roentgen therapy should be regarded as a justifiable method of treatment.

In any discussion of the subject of roentgen treatment of the enlarged thymus the possibility of *late effects* such as

The case which is presented illustrates the finding of a large thymus which at no time gave symptoms in any way referable to compression of the trachea or of other variety which have been attributed previously in the literature to an enlargement of the thymus.

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I wish to express my appreciation and thanks to Dr. John P. Scott for permission to use his case for this discussion.



100 roentgens measured in air is usually recommended. One treatment through an anterior chest portal is employed and if there is no perceptible effect upon the size of the thymus roentgenographically, or in diminution of the symptoms, a second treatment may be given after an interval of one week. Some prefer to give the second treatment through a posterior chest portal. A fenestrated lead shield should be employed to protect the neck, chin and lower portion of the chest. If no reduction in the size of the shadow and no improvement in symptoms occur, it can be assumed that the shadow seen in the roentgenogram is not due to thymic enlargement.

#### SUMMARY

In summarizing the diagnosis and treatment of thymic hyperplasia, the conclusions reached by members of the panel discussion of the American Academy of Pediatrics are most pertinent:

The thymus gland causes symptoms of compression occasionally, but such instances are extremely rare and other causes of compression must be sought before thymic enlargement can be considered the etiologic factor. Certain enlargements of mediastinal structures can cause symptoms of compression which respond to irradiation, but this, too, is of rare occurrence. It can be assumed that whatever knowledge which has been gained experimentally concerning the functions of the thymus is not applicable as yet to the diagnosis and treatment of thymic hyperplasia. Great caution is necessary before a statement can be made that roentgenograms show thymic enlargement. It is well to discard the term "status thymicolymphaticus." If the thymus is related to sudden death it is only in a secondary capacity, and there is no treatment of the thymus by injection of any thymic extract, by irradiation, or by its extirpation which would have any effect upon the prevention of sudden death.

To this should be added especial emphasis upon the necessity of employment of light roentgen dosage. No more than two treatments are necessary to accomplish the desired result and the series of three to six treatments which formerly was employed is now believed to be ill advised.

## ENDOCRINE CONSIDERATION OF THE PANCREAS

JOSEPH T. BEARDWOOD, Jr., M.D., F.A.C.P.\*

THE pancreas has two internal secretions; the first and most important is *insulin*, and the second is a less understood secretion which probably has some slight effect on relieving arterial spasm. Insulin is elaborated by the beta cells of the islands of Langerhans. The exact mechanism of its secretion is not altogether understood.

Alterations in insulin secretion result in two distinct disease entities. The first of these, and by far the most important, is that due to an insufficient secretion of insulin and is called *hypo-insulinism* or *diabetes mellitus*. The second, a widespread condition, is that due to an excessive secretion of insulin and is called *hyperinsulinism*. It is quite possible that the latter condition may occur even more frequently than does diabetes. Its symptomatology is only now beginning to be appreciated.

### DIABETES MELLITUS (HYPO-INSULINISM)

Diabetes, or hypo-insulinism, has been of tremendous historical and scientific interest. Although Cawley in 1788 recorded a case of diabetes which came to autopsy and showed damage to the pancreatic calices, it was not until von Mering and Minkowski<sup>1</sup> in 1899 removed the pancreas of a dog and produced diabetes that the pancreas was definitely linked up with this condition.

For many years there was some dispute as to which part of the pancreas was at fault in this disease; whether it was the acinar portion of the pancreas or the small islands, to which the name "islands of Langerhans" has been attached

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easy. However, there are a large group of other symptoms which should arouse suspicion that diabetes is present. Among these might be listed (1) gradual loss of weight and strength, (2) rapid refractive changes in the eye or early cataracts or in some cases retinal hemorrhage, (3) pruritus, particularly pruritus vulvae, which is often an early and very annoying symptom, (4) intermittent claudication or cramps in the legs, which may be found, not only in the elderly diabetic with arterial changes, but also in the young individual as an early sign; (5) frequent infections that fail to improve in spite of adequate drainage (among the most common are carbuncle and palmar abscesses); (6) impotence, both in the male and female; and, finally, (7) extensive pyorrhea. Indeed we feel that there is probably a specific type of diabetic pyorrhea in which the gums are red and swollen and areas of necrosis extend down over the gingival margin, giving an appearance not unlike Vincent's angina.

It is important to remember that a certain number of diabetics, possibly as many as 15 to 20 per cent, do not know of their diabetes until a complication such as acidosis intervenes, or the urine is examined routinely.

### Diagnosis

The diagnosis of diabetes is, in the final analysis, a laboratory procedure. The finding of sugar in the urine of any person, at any time, should arouse the suspicion that he has diabetes mellitus. About 7 per cent of glycosurics are non-diabetic, and about 10 per cent of true diabetics do not always have sugar in the urine. A blood sugar determination is of inestimable value in clinching the diagnosis. A fasting sugar which is over 120 mg. per 100 cc. of blood should arouse suspicion. In many cases it is more advantageous to make a blood sugar determination two or three hours after a meal which contains 75 to 100 gm. of carbohydrate. If the blood sugar, three hours after such a meal, is over 120 mg. per 100 cc., it is certainly suggestive of diabetes, and if it is over 140 mg. it is pathognomonic. Very rarely, it may be necessary in borderline cases to determine the glucose tolerance, either by the usual three-hour test or the two-dose, one-hour

after their discovery by Langerhans<sup>2</sup> in 1869. In 1901 Opie apparently was able to locate the pancreatic changes seen in diabetes in the islands of Langerhans, although as early as 1893 Laguesse<sup>3</sup> suggested that probably these islands produced an internal secretion. It is interesting that in 1916 Shafer proposed the name "insulin" for the internal secretions of the islands of Langerhans. As yet, insulin was undiscovered. The work of F. G. Banting and C. H. Best<sup>4</sup> in 1921, from which the discovery of insulin resulted, is too well known to require repetition here. It is very interesting that the search for insulin which was carried on from 1889 until its discovery in 1921 resulted in developing the basis of physiological chemistry and much of the present-day knowledge of the subject of metabolism.

The work of Houssay<sup>5</sup> and many other investigators creates some doubt as to whether actual disease of the islands of Langerhans is necessary to produce diabetes. This work opened up the entire field of the endocrinologic physiology of diabetes. Evans<sup>6</sup> recently demonstrated the diabetogenic factors of the anterior pituitary gland and Young<sup>7</sup> has recently shown that if anterior pituitary substance is injected in large amounts, clinical diabetes can be produced experimentally in animals. Beardwood and Rouse<sup>8</sup> more recently reported that the use of estrogenic substances, in large enough doses to suppress the secretion of the anterior pituitary, will often result in an amelioration of the diabetic symptoms. It would seem from the recent work that the entire endocrine system may be involved in diabetes. But whether we believe that actual destruction or impairment of the islet tissue is necessary to produce diabetes, or whether we feel that, even in the presence of a normal insulinogenic system, other factors can produce the symptom complex, the fact remains that insulin, an internal secretion of the pancreas, is the only specific therapeutic agent at our command.

### Symptoms

The usual symptoms of diabetes are increased thirst and urination, loss of weight, loss of strength and increased appetite. Such cardinal symptoms should make the recognition

## Diet

The keystone of diabetic treatment is diet, and all other methods of treatment are secondary. I would like to state at the beginning that in my opinion a qualitative diet, that is, one in which the patient is instructed to eat all of certain foods and none of others, is not advisable. Some method of measurement, be it with scales or household measures, should be used. Measuring cups and spoons are accurate enough for clinical use.

There has been in the past, and still is, some slight difference of opinion as to the ideal type of diet for a diabetic. I think all agree that an adequate amount of protein, amounting to at least 1 gm. of protein per kilogram of ideal body weight, is essential. The distribution of the carbohydrate and fat is still open to debate. However, I feel that for a diabetic whose ideal weight is 135 or 140 pounds a diet of 150 gm. of carbohydrate, 70 gm. of protein and 90 gm. of fat is quite sufficient. The foods need not be weighed but should be measured with household measures. (See attached diet.) As a rule, it is quite satisfactory to divide this diet into three equal meals. However, particularly if protamine insulin is used, it may be necessary to give a fourth meal before retiring, or to redistribute the amount of carbohydrate in relation to the different meals.

It is our custom, unless a patient is in acidosis or unless the diabetes is quite severe, to place him on a diet alone for a short period of time, before considering insulin therapy. This filters out the relatively mild diabetics—that is, those who do not need insulin—and results in the utilization of a smaller dose of insulin for the initial standardization in those who require insulin. It is important also, that the patient be taught to select foods from the standpoint of vitamin and mineral content. There is seldom need for supplementary vitamin feeding if the patient is sufficiently educated to appreciate the importance of including the proper food in his everyday menu. The following diet scheme may be used to measure diets and, while the variety of foods included may not be sufficient for all purposes, it is a very satisfactory initial working basis.

test. However, in most cases, if the blood sugar determination is made after a meal instead of fasting, the sugar tolerance test will not be necessary.

One can often differentiate between renal or benign glycosuria and real diabetes on the basis of a urinary examination alone, if he determines the total amount of glucose excreted in twenty-four hours on a diet poor in carbohydrate, and then, after a rest of a day or so, has the patient take a diet rich in carbohydrate, with large amounts of starches and sugars. If the amount of sugar excreted in the two specimens, expressed in grams, does not vary a great deal the chances are that the patient has benign or renal diabetes.

It should be stressed that neither the diagnosis nor treatment of diabetes requires extensive laboratory facilities. The average case can be carried along with urinalysis alone, and there are few places where it is impossible to secure an occasional blood sugar determination if that is definitely indicated.

### Treatment

The approach to the treatment of the patient with diabetes differs greatly from that in any other disease for which the physician must prescribe. In the first place, it is important to realize that the patient's future, his freedom from complications and his longevity depend entirely on how thoroughly he is instructed about his disease. There is no other pathologic condition in which education of the patient is so important. Diabetics must live with their diabetes for the balance of their lives. How long that is depends largely upon how cooperative they are, and this, in our experience, depends on how careful the physician is in instructing them at the first or second visit. The diabetes can seldom be satisfactorily managed by simply handing the patient a printed diet slip and telling him to read it and follow it. The physician should take time to explain carefully what diabetes is, the measures of treatment, and what is to be expected from such treatment. By so doing, he will obtain a cooperative patient, a patient who responds favorably to therapy, who avoids complications and remains a useful and productive member of society.

Spinach, cooked.....	1 cup
Tomato, fresh.....	1 medium
Tomato, canned or cooked.....	$\frac{3}{4}$ cup
Tomato juice.....	$\frac{1}{2}$ cup
Tomato ketchup.....	2 tablespoonfuls
Turnips, cooked.....	$\frac{3}{4}$ cup
Apricots, water packed.....	3 halves
Avocados.....	$\frac{1}{2}$ , 3 inches long
Cherries, Royal Anne, water packed.....	12
Grapefruit.....	$\frac{1}{2}$ cup
Cantaloupe.....	$\frac{1}{4}$ melon, 5 inches in diameter
Lemon juice.....	$\frac{1}{4}$ cup
Pears, water packed.....	2 halves
Plums, fresh.....	2, $2\frac{1}{2}$ inches in diameter
Strawberries, water packed.....	$\frac{1}{2}$ cup
Tangerine.....	1, 2 inches in diameter
Saltines.....	2
Puffed wheat.....	$\frac{3}{4}$ cup
Puffed rice.....	$\frac{1}{2}$ cup

## GROUP II

(10 Gm. of Carbohydrate and 2 Gm. of Protein)

Beans, lima, canned.....	$\frac{1}{2}$ cup
Carrots, raw.....	cup
Kohlrabi, cooked.....	cup
Peas, canned.....	cup
Peas, fresh.....	cup
Pumpkin, cooked.....	cup
Squash, cooked.....	cup
Orange, E. P.....	1 small
Pineapple, fresh.....	1 slice, $\frac{1}{2}$ inch thick
Peach, fresh.....	1 medium
Strawberries, fresh.....	cup
Watermelon.....	1 cup
Banana.....	1 small
Raspberries, fresh.....	cup
Blackberries, fresh.....	cup
Grapes.....	cup
Oatmeal (dry measure).....	3 tablespoons
Triscuit.....	2, 2 by 2 inches
Uneda biscuits.....	2
Rice krispies.....	cup
Shredded wheat.....	biscuit
Asparagus soup (Campbell's).....	cup
Celery soup.....	cup
Chicken gumbo.....	cup
Clam chowder.....	cup
Cream mushroom.....	cup
Tomato soup.....	cup
Vanilla ice cream.....	pint

## GROUP III

(15 Gm. of Carbohydrate and 3 Gm. of Protein)

Corn, fresh.....	6 level tablespoonfuls
Corn, canned.....	3 rounded tablespoonfuls
Potatoes.....	3 rounded tablespoonfuls



## SIMPLIFIED DIABETIC DIET

*Instructions*

All measurements are level unless otherwise stated. All meat measurements are for the lean part of the meat only. Standard glass measuring cup and standard measuring spoons should be used for measuring the food.

Coffee, tea, fat-free meat broths, mushrooms, lettuce and celery may be taken in any quantity desired because they have little or no food value.

Any fat food may be used for the fat measurements; *i.e.*, butter, olive oil, mayonnaise, meat fat or cream. When cream is used, five times the amount of the fat measurement is needed. If the meal you have chosen requires 1 tablespoonful of fat and you wish to use cream, five tablespoonfuls of cream is the correct amount to use.

You must eat three meals every day. Eat nothing between meals and nothing before going to bed at night. Eat nothing except the food allowed you on your diet.

*Your diet prescription is as follows:*

- Two foods in Group I for each meal
- One food in Group II for each meal
- Two foods in Group III for each meal
- One and one-half foods in Group IV for each meal
- One extra tablespoonful of fat per day

## GROUP I

(5 Gm. of Carbohydrate and 1 Gm. of Protein)

Asparagus, fresh or canned.....	18 tips, 4 inches long
Artichokes, French, canned.....	5 small hearts
Beet greens, cooked.....	1 cup
Broccoli, cooked.....	1 cup
Brussels sprouts, cooked.....	$\frac{3}{4}$ cup
Beans, string, canned.....	1 cup
Beans, string, fresh.....	$\frac{3}{4}$ cup
Beets, cooked.....	$\frac{1}{2}$ cup
Cabbage, cooked.....	1 cup
Cabbage, raw.....	1 $\frac{1}{2}$ cups
Cauliflower, cooked.....	1 cup
Carrots, cooked.....	$\frac{3}{4}$ cup
Celery, raw.....	8 pieces, 9 inches long
Celery, cooked.....	1 $\frac{1}{2}$ cups
Cucumber.....	1 medium
Dandelion, cooked.....	1 cup
Endive.....	3 stalks
Egg plant, cooked.....	$\frac{1}{2}$ cup
Green pepper.....	1 average
Kale, cooked.....	$\frac{1}{2}$ cup
Leeks, cooked.....	1 cup
Lettuce.....	12 average leaves
Okra, cooked.....	1 cup
Onions, cooked.....	$\frac{1}{2}$ cup
Onions, raw.....	1, 2 inches in diameter
Radishes.....	12 average
Rhubarb, cooked.....	2 cups
Sauerkraut, cooked.....	$\frac{1}{2}$ cup

Food	Size (in inches)	Amount of Fat to be Used (in tablespoonfuls)
Clams, "little neck"	10	2
Clams, "cherry-stone"	6	2
Hamburg	2 rounded tablespoonfuls	1
Bologna	$\frac{1}{2}$ inch slice	1
Frankfurter	1 six inches long	1
Pork sausage	2 $\frac{1}{2}$ long, $\frac{1}{2}$ wide, $\frac{1}{2}$ thick	0
Boiled ham	$\frac{1}{2}$ slices	1
Salmon, canned	2 rounded tablespoonfuls	1 $\frac{1}{2}$
Tuna, canned	2 rounded tablespoonfuls	1 $\frac{1}{2}$
Mackerel, fresh	2 $\frac{1}{2}$ long, 2 wide, 2 $\frac{1}{2}$ thick	2
Mackerel, salted	$\frac{1}{2}$ pound	1
American cheese	$\frac{1}{2}$ slices	1
Swiss cheese	2 $\frac{1}{2}$ inch cube	1
Liederkranz cheese	$\frac{1}{2}$ tablespoonfuls	1
Limburger cheese	3 tablespoonfuls	1
Camembert cheese	1 triangle	1
Cottage cheese	$\frac{1}{2}$ tablespoonfuls	1
Philadelphia cream cheese	1 package	1
Roquefort cheese	3 long, 2 $\frac{1}{2}$ wide, $\frac{1}{2}$ thick	1 $\frac{1}{2}$

#### MISCELLANEOUS FOODS

		Group			
		I	II	III	IV
Almonds	20 nuts		1		1
Peanuts	$\frac{1}{2}$ cup		2		1
Walnuts, English	6 nuts	1			1
Walnuts, black	6 nuts	1			1
Milk	1 glass		1		1
Scrapple	$\frac{1}{2}$ pound		1		1
Evaporated milk	$\frac{1}{2}$ cup		1		1
1 Teaspoonful fat					
Buttermilk	1 glass		1		1
Chicken noodle soup (Campbell's)	$\frac{1}{2}$ cup		1		1
Pepper pot soup (Campbell's)	$\frac{1}{2}$ cup		1		1

#### Insulin

If the diabetic on a diet which is adequate for maintenance, that is, adequate for his everyday needs, fails to show marked reduction in the blood sugar or in the amount of sugar in the urine after a given period of trial, insulin is indicated. It is well known that we have no substitute for insulin and that insulin is inactive if given in any other way than by hypodermic injections. It is important to point out that the experimental work of Young, and the clinical work of Root and other investigators, have shown that if we are to keep the diabetic a mild diabetic, and if we are ever to expect a "cure," the sooner the administration of insulin is begun the better the results are apt to be. In other words, if we allow the diab-

Parsnips .....	$\frac{1}{2}$ cup
Pear, fresh .....	1 medium
Orange juice .....	$\frac{1}{2}$ cup
Apple, raw .....	1 medium
Prunes, dried ....	3
Apricots, dried ...	$4\frac{1}{2}$
Peaches, dried ...	3
Huckleberries ..	$\frac{3}{4}$ cup
Cherries, fresh. .	$\frac{1}{2}$ cup
Cream of wheat	$1\frac{1}{2}$ tablespoonfuls
Farina . . .	$1\frac{1}{2}$ tablespoonfuls
Grapenuts	6 teaspoonfuls
Ralston .	$1\frac{1}{2}$ tablespoonfuls
Wheatena .	$1\frac{1}{2}$ tablespoonfuls
Corn flakes.	$\frac{1}{2}$ cup
Rice, cooked.	3 rounded tablespoonfuls
Macaroni, cooked	3 rounded tablespoonfuls
Spaghetti, cooked	3 rounded tablespoonfuls
Noodles, cooked	3 rounded tablespoonfuls
Wheaties ....	$\frac{1}{2}$ cup
Bran flakes ..	$\frac{1}{2}$ cup
Bread, white, whole wheat, rye	1 slice
Hollywood bread	$1\frac{1}{2}$ slices
Jello . . . . .	$\frac{1}{2}$ box
Beans (Campbell's)	$\frac{1}{3}$ cup
Chestnuts, roasted	20

## GROUP IV

(10 Gm. of Protein and 20 Gm. of Fat)

Amount of Fat  
to be Used (in  
tablespoonfuls)

Food	Size (in inches)	
Smoked ham	3 long, $1\frac{1}{2}$ wide, $\frac{1}{2}$ thick	1
Liver ..	$\frac{1}{2}$ long, 3 wide, $\frac{1}{4}$ thick	2
Lamb, veal, chicken, duck	3 long, $3\frac{1}{2}$ wide, $\frac{1}{2}$ thick	$1\frac{1}{2}$
Lamb chop .	2 small	$\frac{1}{2}$
Round steak	$2\frac{1}{2}$ long, 3 wide, $\frac{1}{2}$ thick	2
Sirloin	2 long, 3 wide, $\frac{1}{2}$ thick	$1\frac{1}{2}$
Tenderloin steak	$\frac{3}{4}$ average steak	$1\frac{1}{2}$
Roast or corned beef	$4\frac{1}{2}$ long, $2\frac{1}{2}$ wide, $\frac{1}{2}$ thick	$1\frac{1}{2}$
Pork, chops or roast	2 long, 2 wide, $\frac{1}{2}$ thick	$1\frac{1}{2}$
Kidney or tripe.	2 long, 3 wide, $\frac{1}{2}$ thick	2
Tongue	6 slices	$\frac{1}{2}$
Squab	$\frac{1}{2}$ average	1
Turkey	3 long, 3 wide, $\frac{1}{2}$ thick	1
Sweetbreads	$2\frac{1}{2}$ long, 3 wide, $\frac{1}{2}$ thick	$1\frac{1}{2}$
Eggs .	2	1
Bacon	5 strips (cooked crisp)	0
Bacon and egg	1 egg and $2\frac{1}{2}$ strips bacon	$1\frac{1}{2}$
Salmon or codfish	2 long, 2 wide, $\frac{1}{2}$ thick	$1\frac{1}{2}$
Halibut or whitefish	$2\frac{1}{2}$ long, 2 wide, $2\frac{1}{2}$ thick	2
Trout or shad	2 long, $\frac{1}{2}$ wide, $1\frac{1}{2}$ thick	$1\frac{1}{2}$
Weakfish, haddock, flounder	2 long, 2 wide, $1\frac{1}{2}$ thick	2
Sardines .	6	$1\frac{1}{2}$
Crab meat .....	$\frac{3}{4}$ cup	2
Shrimp, fresh	8 ..	$1\frac{1}{2}$
Scallops, fresh, small	8	$1\frac{1}{2}$
Oysters, Blue point	10	1
Lobster, flaked	$\frac{1}{2}$ cup	

Food	Size (in inches)	Amount of Fat to be Used (in tablespoonfuls)
Clams, "little neck".....	10.....	2
Clams, "cherrystone".....	6.....	2
Hamburg.....	2 rounded tablespoonfuls.....	1½
Bologna.....	½ inch slice.....	1
Frankfurter.....	1 six inches long.....	1
Pork sausage.....	2½ long, ½ wide, 3 thick.....	0
Boiled ham.....	4 slices.....	2
Salmon, canned.....	2 rounded tablespoonfuls.....	1½
Tuna, canned.....	2 rounded tablespoonfuls.....	1½
Mackerel, fresh.....	2½ long, 2 wide, 2½ thick.....	2
Mackerel, salted.....	½ pound.....	1
American cheese.....	4 slices.....	1
Swiss cheese.....	2½ inch cube.....	1
Liederkrantz cheese.....	4 tablespoonfuls.....	1
Limburger cheese.....	3 tablespoonfuls.....	1
Camembert cheese.....	1 triangle.....	1
Cottage cheese.....	4 tablespoonfuls.....	1½
Phila. cream cheese.....	1 package.....	1
Roquefort cheese.....	3 long, 2½ wide, ½ thick.....	1½

# MISCELLANEOUS FOODS

		Group			
		I	II	III	IV
Almonds.....	20 nuts.....		1.....		1
Peanuts.....	½ cup.....		2.....		1
Walnuts, English.....	6 nuts.....	1.....			1
Walnuts, black.....	6 nuts.....	1.....			1
Milk.....	1 glass.....		1.....		1
Scrapple.....	½ pound.....		1.....		1
Evaporated milk.....	½ cup.....		1.....		1
1 Teaspoonful fat					
Buttermilk.....	1 glass.....	1.....			1
Chicken noodle soup (Campbell's).....	½ cup.....	1.....			1
Pepper pot soup (Campbell's).....	½ cup.....	1.....			1

## Insulin

If the diabetic on a diet which is adequate for maintenance, that is, adequate for his everyday needs, fails to show marked reduction in the blood sugar or in the amount of sugar in the urine after a given period of trial, insulin is indicated. It is well known that we have no substitute for insulin and that insulin is inactive if given in any other way than by hypodermic injections. It is important to point out that the experimental work of Young, and the clinical work of Root and other investigators, have shown that if we are to keep the diabetic a mild diabetic, and if we are ever to expect a "cure," the sooner the administration of insulin is begun the better the results are apt to be. In other words, if we allow the diab-

Parsnips.....	$\frac{1}{2}$ cup
Pear, fresh.....	1 medium
Orange juice.....	$\frac{1}{2}$ cup
Apple, raw.....	1 medium
Prunes, dried.....	3
Apricots, dried.....	$4\frac{1}{2}$
Peaches, dried.....	3
Huckleberries.....	$\frac{3}{4}$ cup
Cherries, fresh.....	$\frac{1}{2}$ cup
Cream of wheat.....	$1\frac{1}{2}$ tablespoonfuls
Farina.....	$1\frac{1}{2}$ tablespoonfuls
Grapenuts.....	6 teaspoonfuls
Ralston.....	$1\frac{1}{2}$ tablespoonfuls
Wheatena.....	$1\frac{1}{2}$ tablespoonfuls
Corn flakes.....	$\frac{1}{2}$ cup
Rice, cooked.....	3 rounded tablespoonfuls
Macaroni, cooked.....	3 rounded tablespoonfuls
Spaghetti, cooked.....	3 rounded tablespoonfuls
Noodles, cooked.....	3 rounded tablespoonfuls
Wheaties.....	$\frac{1}{2}$ cup
Bran flakes.....	$\frac{1}{2}$ cup
Bread, white, whole wheat, rye.....	1 slice
Hollywood bread.....	$1\frac{1}{2}$ slices
Jello.....	$\frac{1}{8}$ box
Beans (Campbell's).....	$\frac{1}{2}$ cup
Chestnuts, roasted.....	20

## GROUP IV

(10 Gm. of Protein and 20 Gm. of Fat)

Amount of Fat  
to be Used (in  
tablespoonfuls)

Food	Size (in inches)	
Smoked ham.....	3 long, $1\frac{1}{2}$ wide, $\frac{1}{2}$ thick...	1
Liver.....	4 long, 3 wide, $\frac{1}{4}$ thick....	2
Lamb, veal, chicken, duck.....	3 long, $3\frac{1}{2}$ wide, $\frac{3}{4}$ thick....	$1\frac{1}{2}$
Lamb chop.....	2 small.....	$\frac{1}{2}$
Round steak.....	$2\frac{1}{2}$ long, 3 wide, $\frac{1}{2}$ thick....	2
Sirloin.....	2 long, 3 wide, $\frac{1}{2}$ thick....	1
Tenderloin steak.....	$\frac{3}{4}$ average steak.....	$\frac{1}{2}$
Roast or corned beef.....	$4\frac{1}{2}$ long, $2\frac{1}{2}$ wide, $\frac{1}{2}$ thick....	$\frac{1}{2}$
Pork, chops or roast.....	2 long, 2 wide, $\frac{1}{2}$ thick....	2
Kidney or tripe.....	2 long, 3 wide, $\frac{1}{2}$ thick....	$\frac{1}{2}$
Tongue.....	6 slices.....	1
Squab.....	$\frac{1}{4}$ average.....	1
Turkey.....	3 long, 3 wide, $\frac{1}{2}$ thick....	$1\frac{1}{2}$
Sweetbreads.....	$2\frac{1}{2}$ long, 3 wide, $\frac{1}{2}$ thick....	1
Eggs.....	2.....	0
Bacon.....	5 strips (cooked crisp)....	$\frac{1}{2}$
Bacon and egg.....	1 egg and $2\frac{1}{2}$ strips bacon....	$1\frac{1}{2}$
Salmon or codfish.....	2 long, 2 wide, $\frac{1}{2}$ thick....	2
Halibut or whitefish.....	$2\frac{1}{2}$ long, 2 wide, $2\frac{1}{2}$ thick....	$1\frac{1}{2}$
Trout or shad.....	2 long, 4 wide, $1\frac{1}{2}$ thick....	2
Weakfish, haddock, flounder.....	2 long, 2 wide, $1\frac{1}{2}$ thick....	$1\frac{1}{2}$
Sardines.....	6.....	2
Crab meat.....	$\frac{3}{4}$ cup.....	$1\frac{1}{2}$
Shrimp, fresh.....	8.....	$1\frac{1}{2}$
Scallops, fresh, small.....	8.....	$1\frac{1}{2}$
Oysters, blue point.....	10.....	1
Loebster, flaked.....	$\frac{1}{2}$ cup.....	

If a patient is satisfactorily standardized on regular insulin, taking more than one dose a day, he is entitled to a trial of protamine or another of the long-acting insulins as a substitute. It is important to remember that protamine offers no advantages over regular insulin beyond its requirement of fewer injections. As a rule, if the patient was taking three doses or more of regular insulin a day, we continue with the same morning dose of regular insulin and give 80 per cent of the balance as protamine insulin in the evening before dinner. If the patient is taking only two doses of insulin a day, we give 80 per cent of the total dose of insulin as protamine in the morning, and continue for a few days with the regular insulin (20 per cent of the dose) as a supplementary injection. In the use of protamine insulin, it is important to remember that, after a period of five or ten days, the utilization of the insulin improves and the dosage may be very definitely reduced. Crystalline insulin, or the solution of insulin crystals, falls probably half way between regular and protamine insulin in its duration of action and has a definite use in the patient who is allergic to insulin.

### Insulin Reaction

With *regular insulin* the reaction occurs usually from two to five hours after the injection. The symptoms are hunger, weakness, sweating, tremor, nervousness which may progress to certain mental symptoms of aphasia, diplopia, emotional instability, difficulty in answering rapidly or a scanning type of speech which may be followed at times by unconsciousness, convulsions, or even death.

Reactions occurring following the use of *protamine insulin* occur from twelve to twenty-four hours after the injection of the insulin—usually about eighteen hours. It is important to remember that in these cases the blood sugar drops slowly and that the patient is not very apt to have the protective adrenal mechanism and the usual symptoms of insulin reaction are absent. The symptoms most frequently found in the protamine insulin reaction are headache, aphasia, disorientation, convulsions and unconsciousness. When a reaction occurs the blood sugar is apt to be very low, possibly even

etes to run its course, poorly controlled, for an indefinite period of time, certain changes take place in the pancreas which are irreversible; whereas, if insulin therapy is instituted early, or if the pancreas is "splinted" satisfactorily by proper diet and insulin, it tends to show a return to normal function.

The type of insulin employed and the method of arriving at initial dosages vary with the individual case. The goal to strive for is to standardize the patient on the smallest possible number of injections of insulin a day and to fit the insulin therapy into his normal routine insofar as is commensurate with adequate control. Ideally, it is more satisfactory to standardize the patients on regular insulin and then shift to protamine or some of the other long-acting insulins, although it is possible at times to start with protamine insulin if the diabetes is not particularly severe.

A rough method that we have used for determining the initial daily dose of *regular insulin* is to place the patient on a maintenance diet without insulin for a few days, then determine the average blood sugar reading and divide by five; this will give the initial daily dosage of insulin. If the dosage so obtained is more than 20 units, it is divided and given twice a day, if more than 40 units, three times a day, and more than 50 units, possibly four or five times a day. Blood sugar determinations are made twice a day or urinalysis is done before meals and on retiring at night, and the dosage is adjusted depending upon the findings. It is important to realize that, whatever method one uses for determining the initial dose of insulin, the final dose for satisfactory standardization will vary with each case. The important thing is to have a satisfactory formula for calculating the initial dose.

In the use of *protamine insulin*, somewhat the same formula may be utilized. All the protamine insulin may be given at one time, in the morning; however, if the amount to be given is more than 50 units the balance needed to make up the total requirement may be given as regular insulin. If blood sugar determinations are not available the old method of giving one unit of insulin for each 2 gm. of glucose excreted in the urine in twenty-four hours may be practiced.

should be avoided if at all possible. If these reactions occur it usually means that some change must be made in the insulin dosage or in another phase of the program of the diabetic.

*Insulin Allergy.*—There are seen, at times, patients allergic to insulin who develop localized areas of itching and urticaria which in rare instances may extend to a generalized urticaria. Fortunately, these cases are rare, although it is not at all uncommon in the use of protamine insulin to find that localized swelling at the site of injection occurs. This will in most instances disappear with the continued use of the protamine.

### HYPERINSULINISM

In hyperinsulinism, the antithesis of diabetes, an excessive amount of insulin is produced in response to normal stimuli as a result of an alteration in the regulation of insulin production. Such alteration results in spontaneous hypoglycemia with characteristic symptoms which will be discussed later. The entire clinical picture of hyperinsulinism is due to overactivity of the beta cells of the islands of Langerhans or to tumors of the islands, benign or malignant, made up for the most part of beta cells. The writings of Harris in 1924 and subsequently have done much to point out the condition of hyperinsulinism, which is not uncommon. Most of the cases fall into the functional group in which symptoms are seldom severe enough to cause the patients to seek medical advice. It is only the patients who present rather severe symptoms who feel it necessary to consult a physician.

Spontaneous hypoglycemia and symptoms of hyperinsulinism may be due to other endocrinopathy than that of the pancreas. The pituitary, thyroid, liver, adrenal and at times the sex glands may through alteration in hormonal balance produce a condition of hypoglycemia. It is important that these other glands be ruled out as sources before one attributes the picture of hyperinsulinism to the pancreas alone.

There are two types of hyperinsulinism which are recognized clinically. One is due to actual tumor of the islands of Langerhans and the other is the so-called functional type in which very little alteration can be demonstrated in the islet structure.



below 40 mg. per 100 cc. It is also important to remember that, in the reaction caused by regular insulin, if the patient is given carbohydrate in some form an immediate return to a normal blood sugar level occurs and the level remains at normal or higher. In the reaction due to protamine insulin, however, even if we restore the blood sugar to normal by using some form of carbohydrate, there may still be in the body a large amount of insulin which as yet has not acted, and the patient is apt to experience a second reaction of equal or greater severity. If a protamine insulin reaction occurs of sufficient severity to cause symptoms, it is far better to give 20 to 30 mg. of carbohydrate every half hour or hour for three or four hours until the patient has entirely recovered. These reactions frequently occur at night during sleep and the patient will have convulsions without awaking. He is likely to complain in the morning of headache and stiffness of the neck, the result of the convulsive seizures through the night.

Reactions occurring with *crystalline insulin* or a solution of insulin crystals are closely similar to those occurring with regular or amorphous insulin.

*Treatment.*—The treatment of insulin reaction of any type, of course, is to give the patient carbohydrate or glucose in some form. If, after an adequate amount is given, the patient does not react satisfactorily, it is important to look for other causes for the symptoms. The glucose can be given by mouth as ginger ale, orange juice, karo syrup, or, if the patient is totally unconscious, it may be given by vein as a 50 per cent solution. If the patient is unconscious because of hypoglycemia and intravenous glucose is given, a very dramatic recovery results. If it is not feasible to use the intravenous route, glucose may be given by a stomach tube or a Jutte duodenal tube introduced through the nose. Glucose or sugar given by rectum is not satisfactorily absorbed and is often without value. Oftentimes a patient who is unconscious and cannot swallow can be made sufficiently alert to permit the administration of fluids by mouth by giving hypodermically 10 to 15 minims of adrenalin solution.

An insulin reaction is, at times, a very serious matter and

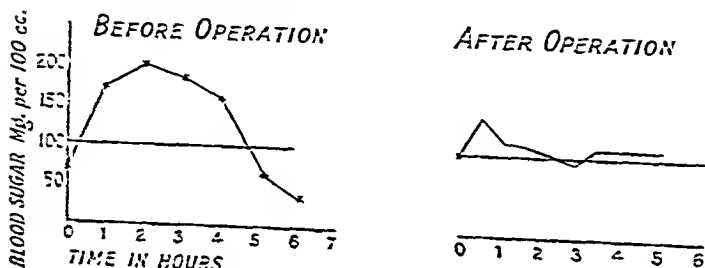
## Diagnosis

The important diagnostic criteria are:

1. A low fasting blood sugar level, usually below 60 mg. per 100 cc.
2. A blood sugar level below 50 mg. per 100 cc. during an attack
3. The dramatic relief of symptoms by the intravenous injection of glucose
4. The glucose tolerance test

Before the *glucose tolerance test* is undertaken it is important that the patient be on a diet sufficiently high in carbo-

*E.S., MALE—32 YRS.*



*M.J., FEMALE—53 YRS.*

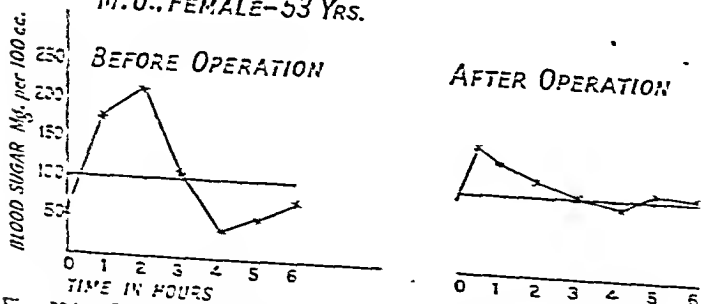


Fig. 226.—Glucose tolerance curves before and after operation in two cases of pancreatic adenoma.

hydrate to avoid any influence that undernutrition might have on the curve. It is important in appraising diagnostic tests for hyperinsulinism to remember that the flat plateau type of curve, even if the blood sugar readings are continuously

## Symptoms

The symptoms of hyperinsulinism as a rule appear rather gradually over a period of months or years and may be accompanied by remissions and acute exacerbations. Occasionally, however, and this is particularly true in the case of tumors, the symptoms are rather sudden in their onset and progressive in their severity. The earlier and milder attacks usually present the symptoms of sweating, flushing, pallor, chilliness, hunger, epigastric pain, dizziness, weakness, tendency to syncope, palpitation and tachycardia. As these progress it is not unusual to find psychiatric manifestations such as emotional instability, apprehension, disorientation, difficulty in concentration, amnesia, mania, unconsciousness preceded by, *at times*, diplopia, thick speech and convulsions. In extreme cases coma may result in death. As a rule these attacks occur early in the morning before breakfast or from three to four hours after eating. They at times are precipitated by unusual physical activity or by an undue delay in meals.

Many of these patients will complain of headache, *difficulty in concentration*, emotional instability, personality change and a series of vague complaints which are poorly expressed, and it is small wonder that neurasthenia is a frequent diagnosis. The condition in those who have gone into the convulsive state has been diagnosed in many instances as epilepsy. A *large number* of these individuals have found out that by taking a certain amount of carbohydrate they can be relieved of their symptoms, and if the carbohydrate so chosen, as in one of our cases, is beer it is easy to understand why the laity might be excused for assuming the symptoms to be due to alcoholism.

Physical examination of these patients during an attack will show a tachycardia, an increased blood pressure, flushing of the skin which is usually moist, tremor and accentuation of the tendon reflexes. Babinski's sign is invariably present.

and will probably tide over the seizures which may occur through the night. If the patient is taking much exercise this may have to be compensated for by increasing the diet before exercising.

2. DRUGS.—There is no drug except adrenalin which has any effect on raising the blood sugar, and this effect is evanescent. John has suggested giving small doses of insulin before meals to prevent the pancreas from being overstimulated, and in his hands this procedure has had good results. However, other investigators have not been so fortunate. Sedatives may help in that they cause a lessening of physical exertion, thereby conserving energy and reducing the utilization of carbohydrates.

3. SURGERY.—A conservative regimen should be followed in all cases, whether or not a tumor is suspected, for a sufficient length of time to determine whether it alone will improve the condition.

If in spite of a period of medical treatment the symptoms persist or become more acute and repeated sugar tolerance tests show a curve with a high rise and a sudden drop in the blood sugar readings, the question of exploratory operation should be considered. If a tumor is found, there are few conditions in which surgery gives such gratifying and dramatic results. The technic of the surgical procedure is not in the province of this paper, but it is important to point out that unless a tumor is found partial pancreatectomy will seldom produce relief of symptoms. Most of these tumors are in the pancreas itself, although some are extrapancreatic. They have an orange color which is rather characteristic.

The mortality rate of the exploratory operation is very low.

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low, is not the type seen in hyperinsulinism. The mechanism which accounts for the clinical picture and symptomatology is due to the fact that the blood sugar will drop from normal or slightly elevated level to a very low level and unless this drop occurs the diagnosis of hyperinsulinism is very difficult to substantiate. In making the tests it is important to carry them out to the fifth or sixth hour to make sure that the drop will be detected. If we simply continue the test for two or three hours we often will miss many cases of hyperinsulinism because at the end of the third hour the blood sugar reading is likely to be a little above the accepted level.

Figure 226a shows the glucose tolerance curves in two cases of pancreatic adenoma, proved at operation, which we had on our services at the Abington and Graduate Hospitals.

The differential diagnosis between the functional type of hyperinsulinism and that due to pancreatic adenoma is most important. I feel that there is no adequate test which in a single reading can differentiate these conditions and no attempt should be made to so differentiate until a patient has been observed over a period of time. Conservative treatment should be tried in all cases before operation is considered.

### Treatment

1. DIET.—The ideal diet is one low in carbohydrate in which the carbohydrate is supplied to the patient in 3 per cent and 6 per cent vegetables and fruit. With such a diet absorption from the intestinal tract will be slow, with no great stimulation to the production of insulin such as obtains when a more concentrated carbohydrate diet is followed. For the average adult male a diet of possibly 70 to 80 gm. of carbohydrate, 70 to 90 gm. of protein and 100 to 150 gm. of fat would be the ideal. It may be necessary early in the treatment to supplement this diet with feedings midway between meals but it is important to discontinue these as soon as possible because they in themselves tend to precipitate hypoglycemia by absorption of somewhat concentrated sugars. Many patients will have a much more comfortable night than otherwise if, before retiring, they take a glass of milk to which a tablespoonful of lactose has been added. The lactose is more slowly converted than ordinary sugar

## DIAGNOSIS AND TREATMENT OF DISORDERS OF THE ADRENAL GLANDS

F. D. W. LUKENS, M.D.

In 1940, Kepler and Rynearson<sup>1</sup> discussed diseases of the adrenal glands in these pages. Since then, Thorn's<sup>2</sup> presentation of the treatment of Addison's disease has summarized his wide experience in practical form. Recently, Kepler and Willson<sup>3</sup> and Kepler and Keating<sup>4</sup> and others<sup>5, 6, 7</sup> have fully reviewed the extensive literature on the adrenals. The present article will outline the recent developments in the field of adrenal disease with the understanding that it should be supplemented by reference to more complete reports.

In 1895, extracts of the adrenal medulla were found to raise the blood pressure but it was not until 1927 that extracts of the adrenal cortex were prepared which would prolong the life of adrenalectomized animals. The first discovery led to the present knowledge of the sympathicomimetic amines, such as adrenalin, ephedrine and benzedrine. The finding of active adrenal cortical extracts has been followed by an endless procession of new observations in the fields of chemistry, physiology and medicine. Although many problems remain to be solved, it is now possible to offer a classification of adrenal functions which is based on physiological facts and to which the various clinical disorders can be tentatively related.

Table 1 indicates the chief functions of the adrenal glands and suggests how they may be related to clinical conditions. The major activity of the adrenal medulla needs no comment, but the division of adrenal cortical function into three types is the result of recent investigations with the adrenal steroids.

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increased catabolism of protein and fat and changes in the glycogen content of the liver and muscles have been observed to follow the use of these substances in animals. They prevent the development of hypoglycemia. The occurrence of all these changes emphasizes the profound influence of the adrenal cortex on carbohydrate metabolism which had been previously demonstrated by the extirpation of these glands.<sup>8</sup> *Corticosterone* appears as the representative of this group. The word "diabetogenic" refers to the laboratory testing of these compounds which increase the glycosuria of partially depancreatized rats. They are not known to cause clinical diabetes. The work test, particularly as devised by Ingle, has been of help in studying these steroids. Just as Loeb<sup>9</sup> showed that the defective regulation of sodium was benefited by the ingestion of salt, so Ingle and Lukens<sup>10</sup> have shown that the administration of glucose will restore the animal's capacity to work as effectively as the injection of those hormones which control glucose production. In both cases the use of the substance—sodium or glucose—regulated by the hormone does much to remedy the deficiency of hormone.

(c) Some of the adrenal steroids have androgenic or estrogenic activity, although they are less potent per milligram than the hormones of the gonads. There are no sexual symptoms due to adrenal deficiency beyond those which are attributed to the general weakness of this condition. On the other hand, the excessive or abnormal secretion of adrenal cortical tumors is associated with striking sexual abnormalities.

Most of the adrenal steroids possess at least traces of all three functions (sex, metabolism, electrolyte regulation), and it is not possible to make a rigid qualitative distinction between chemical structure and function. Thorn, Engle and Lewis<sup>11</sup> have made a detailed analysis of these relationships. As an example, a large dose of desoxycorticosterone has almost no metabolic effect and a metabolic hormone (Kendall's compound E) has negligible life maintaining activity. It therefore seems practical to consider the dominant functions of the adrenals as outlined. *When adrenal disease is suspected the physician should first inquire what are the manifestations of sexual, metabolic and electrolyte dysfunction in the patient.*



TABLE 1  
FUNCTIONS OF THE ADRENALS

Site	Major Activity	Chemical Substances	Effects	
			Physiological	Clinical
Medulla	Sympathomimetic	Epinephrine	Pressor action	Pheochrom cytoma Neuroblastoma
Cortex	Water and salt regulation	Desoxycorticosterone	Life maintenance Sodium retention	Deficiency = Addison's disease
	Metabolism	Corticosterone	Diabetogenic Work test	Cushing's Syndrome?
	Sex	Androgens Estrogens	Male and female sex activity	Virilism (women) Feminism (men)

### CHEMISTRY AND PHYSIOLOGY

Almost thirty substances obtained from the adrenal cortex have been identified chemically. They have the sterol nucleus and are known as *adrenal cortical steroids*.

(a) A number of these steroids have the power of increasing the retention of sodium chloride and water by the body. The recently synthesized *desoxycorticosterone acetate* is the most potent in this respect and, in Table 1, has been selected to represent this function. Desoxycorticosterone is also the most effective agent for maintaining the life of adrenalectomized animals. In addition, it restores renal function, maintains a normal level of blood urea and a normal blood volume, thus correcting the hemoconcentration of adrenal insufficiency and the hypotension which may be present. It is effective therapy for most, but not all of the symptoms of Addison's disease in man. Desoxycorticosterone by itself fails to prevent the occurrence of hypoglycemic episodes, although hypoglycemia is less likely to intervene in the patients who are able to eat a normal balanced diet because of this treatment.

(b) There are four compounds, characterized chemically by the presence of oxygen at carbon atom 11 of the sterol ring, which exert the metabolic effects of the adrenal cortex. The broad term "metabolism" is used in Table 1 pending further knowledge of this metabolic activity. At present an

as 50 per cent of cases. This fact, combined with improved treatment, promises a greater life expectancy for many of these patients.

*Diagnosis.*—The diagnosis of Addison's disease still depends primarily on the observation of the classical symptoms—*anorexia, nausea, vomiting, epigastric distress, loss of weight, pigmentation, hypotension and occasionally hypoglycemia.* The writer has been impressed with the flaccidity of the muscles in this condition. Palpation of the muscles may reveal their tone to be as poor as in the late stages of a wasting fever. In typical cases the symptoms will be accompanied by an elevation of the blood urea nitrogen, a reduction in serum chloride, and, if the methods are available, a low serum sodium and elevated serum potassium may be found. The fasting blood sugar may be normal or low. In crisis these changes are marked and the patient is in a state of collapse.

The diagnosis is not difficult when the typical symptoms and findings are present. On the other hand, it is very difficult to establish mild adrenal insufficiency as a cause of vague weakness or indigestion. The following methods have been used in *borderline cases*: (1) The restriction of the dietary intake of sodium chloride to induce the symptoms of addisonian crisis. (2) The test of Cutler, Power and Wilder<sup>12</sup> which standardizes the quantity of sodium and potassium administered for a period of fifty-two hours and employs the urinary chloride excretion as the criterion of insufficiency. This method is fairly accurate but requires time, care and special chemical analyses. Both methods expose the patient to the danger of acute adrenal insufficiency. (3) The response of patients to specific treatment. (4) The tolerance to the ingestion of potassium, which has been difficult to conduct and interpret.

To eliminate these difficulties in borderline cases Robinson, Power and Kepler<sup>13</sup> have developed two tests which are conducted together as follows: The day preceding the test the patient eats the usual three meals but omits extra salt. After 6 P.M. he does not eat or drink. At 10:30 P.M. he voids and discards the urine. All urine voided between 10:30 P.M. and 7:30 A.M. is collected, the volume of this "night

The detailed study of each major adrenal function can then be adapted to the particular needs of the patient.

#### DISEASES OF THE ADRENAL MEDULLA

There is no recognized syndrome due to *medullary deficiency* although the pigmentation of Addison's disease has been attributed to the destruction of the medulla.

##### Pheochromocytomas

Pheochromocytomas are the usually benign tumors of the adrenal medulla which secrete adrenalin. Kepler and Keating<sup>4</sup> cite 103 reported cases. The characteristic symptoms are paroxysms of hypertension, tachycardia, vasomotor disturbances, sweating, nausea, headache and glycosuria. At first the patient may remain well between attacks, but later the symptomatology may become quite varied and a few instances of continuous hypertension have been reported. The diagnosis is difficult especially if the patient is not observed during an attack. Symptoms can sometimes be induced by pressure over the site of the tumor or by bending the body in various positions but such procedures are not without danger. Roentgenologic aids in diagnosis are the same as those used for other adrenal tumors (see Table 3) and must be conducted with appropriate care. The *treatment* is surgical removal of the tumor, which is a difficult operation but which has been followed by recovery when successful.

##### Malignant Tumors

*Neuroblastoma* is an example of the several types of malignant tumor without endocrine activity which arise from medullary tissue. About 270 cases of this group of neuroblastomas, sympatheticoblastomas, neurocytomas and the like have been reported.<sup>4</sup>

#### ADDISON'S DISEASE (ADRENAL INSUFFICIENCY)

*Pathology.*—It was formerly stated that 90 per cent of Addison's disease was due to tuberculosis of the adrenals. Recently evidence has been presented<sup>3</sup> that adrenal insufficiency is due to primary atrophy of the adrenal cortex in as many

adequate carbohydrate ingestion, and specific hormone therapy. The regimen will vary according to the severity of the disease. Thus, *mild* Addison's disease may be controlled by the daily ingestion of 5 to 15 gm. of sodium chloride daily. This is given as 1-gm. enteric-coated tablets, which are best taken with meals, or in solution (e.g., sodium chloride 10 gm., sodium citrate 5 gm., lemon juice 80 cc., sugar 160 gm. with cold water to make 1000 cc.). If the disease is more severe a low potassium diet combined with salt therapy may control the symptoms. The preparation of this diet<sup>14</sup> is not unduly difficult but with the modern improvements in hormone therapy it will be avoided by most patients. *Moderately severe* Addison's disease is controlled by sodium chloride treatment supplemented by hormone treatment at intervals. For example, the patient may remain in good health on 10 gm. of salt daily and 5 cc. of cortical hormone once a week. It requires four to six weeks of hospital observation to work out such a regimen and this care is necessary if the danger of crisis from reduced dosage is to be avoided. Finally, the most severe cases of the disease require continued hormone therapy. The dose of sodium chloride will be adjusted to the type of hormone treatment which includes such possibilities as the following: (1) 5 cc. of cortical extract twice daily with 5 to 15 gm. of sodium chloride; (2) 5 mg. of desoxycorticosterone acetate in oil daily with not more than 5 gm. of sodium chloride daily; (3) pellets of desoxycorticosterone acetate implanted subcutaneously. Pellets are not yet on the market but Thorn has found them satisfactory.

The treatment of addisonian *crisis* must be initiated promptly, avoiding all unnecessary manipulations of the patient who is in collapse. In Table 2 the procedure advised by Thorn<sup>2</sup> has been abstracted and requires only the reminder that each patient will react differently. For example, if crisis has been precipitated by an acute infection, it is possible that after recovery from the infection final maintenance on salt therapy alone will be possible.

EFFECTS OF OVERTREATMENT.—When sodium chloride alone is used, edema has been observed, although the gastro-

urine" is measured and it is saved for chemical analysis should that be necessary. At 8:30 A.M. the patient voids (if possible) and discards the urine. Immediately after this he is given 20 cc. of water per kilogram of body weight within forty-five minutes. He then voids hourly for four hours, i.e., at 9:30, 10:30 and 11:30 A.M. and at 12:30 P.M. The volume of each hourly specimen is measured and the largest of the four specimens is the "volume of day urine" used in subsequent calculations. At 11:30 or 12:30 blood is taken for chemical analysis of the plasma if this appears indicated by the results already obtained from the diuresis test. *It has been found that if the volume of night urine is less than the volume of urine voided at any one hour during the morning, the patient does not have Addison's disease. This has been true of all cases studied.* If, however, the volume of the night urine is greater than the volume voided during any single morning hour, the patient may or may not have Addison's disease and the second procedure become necessary.

The second part of the test includes the determination of the following ratio calculated from the four chemical analyses:

$$A = \frac{\text{Urea in night urine}}{\text{Urea in plasma}} \times \frac{\text{Chloride in plasma}}{\text{Chloride in night urine}} \times \frac{\text{Vol. of day urine (cc.)}}{\text{Vol. of night urine (cc.)}}$$

In calculating this ratio the concentrations of urea and chloride must be expressed in the same unit (e.g., mg. per 100 cc.) throughout the equation. In nearly all instances in which the value for A is 25 or less the patient has Addison's disease. Values for A of more than 30 indicate the absence of Addison's disease. This test is abnormal in the presence of nephritis which should be excluded by the general clinical picture. The value of this new procedure in general practice has not yet been established.

#### Treatment of Addison's Disease

The goal of treatment in adrenal insufficiency is the maintenance of the patient in good health by means of the proper combination of sodium chloride therapy, low potassium diet,

adequate carbohydrate ingestion, and specific hormone therapy. The regimen will vary according to the severity of the disease. Thus, *mild* Addison's disease may be controlled by the daily ingestion of 5 to 15 gm. of sodium chloride daily. This is given as 1-gm. enteric-coated tablets, which are best taken with meals, or in solution (e.g., sodium chloride 10 gm., sodium citrate 5 gm., lemon juice 80 cc., sugar 160 gm. with cold water to make 1000 cc.). If the disease is more severe a low potassium diet combined with salt therapy may control the symptoms. The preparation of this diet<sup>14</sup> is not unduly difficult but with the modern improvements in hormone therapy it will be avoided by most patients. *Moderately severe* Addison's disease is controlled by sodium chloride treatment supplemented by hormone treatment at intervals. For example, the patient may remain in good health on 10 gm. of salt daily and 5 cc. of cortical hormone once a week. It requires four to six weeks of hospital observation to work out such a regimen and this care is necessary if the danger of crisis from reduced dosage is to be avoided. Finally, the most severe cases of the disease require continued hormone therapy. The dose of sodium chloride will be adjusted to the type of hormone treatment which includes such possibilities as the following: (1) 5 cc. of cortical extract twice daily with 5 to 15 gm. of sodium chloride; (2) 5 mg. of desoxycorticosterone acetate in oil daily with not more than 5 gm. of sodium chloride daily; (3) pellets of desoxycorticosterone acetate implanted subcutaneously. Pellets are not yet on the market but Thorn has found them satisfactory.

The treatment of addisonian *crisis* must be initiated promptly, avoiding all unnecessary manipulations of the patient who is in collapse. In Table 2 the procedure advised by Thorn<sup>2</sup> has been abstracted and requires only the reminder that each patient will react differently. For example, if crisis has been precipitated by an acute infection, it is possible that after recovery from the infection final maintenance on salt therapy alone will be possible.

EFFECTS OF OVERTREATMENT.—When sodium chloride alone is used, edema has been observed, although the gastro-

urine" is measured and it is saved for chemical analysis should that be necessary. At 8:30 A.M. the patient voids (if possible) and discards the urine. Immediately after this he is given 20 cc. of water per kilogram of body weight within forty-five minutes. He then voids hourly for four hours, i.e., at 9:30, 10:30 and 11:30 A.M. and at 12:30 P.M. The volume of each hourly specimen is measured and the largest of the four specimens is the "volume of day urine" used in subsequent calculations. At 11:30 or 12:30 blood is taken for chemical analysis of the plasma if this appears indicated by the results already obtained from the diuresis test. *It has been found that if the volume of night urine is less than the volume of urine voided at any one hour during the morning, the patient does not have Addison's disease. This has been true of all cases studied.* If, however, the volume of the night urine is greater than the volume voided during any single morning hour, the patient may or may not have Addison's disease and the second procedure become necessary.

The second part of the test includes the determination of the following ratio calculated from the four chemical analyses:

$$A = \frac{\text{Urea in night urine}}{\text{Urea in plasma}} \times \frac{\text{Chloride in plasma}}{\text{Chloride in night urine}} \times \frac{\text{Vol. of day urine (cc.)}}{\text{Vol. of night urine (cc.)}}$$

In calculating this ratio the concentrations of urea and chloride must be expressed in the same unit (e.g., mg. per 100 cc.) throughout the equation. In nearly all instances in which the value for A is 25 or less the patient has Addison's disease. Values for A of more than 30 indicate the absence of Addison's disease. This test is abnormal in the presence of nephritis which should be excluded by the general clinical picture. The value of this new procedure in general practice has not yet been established.

#### Treatment of Addison's Disease

The goal of treatment in adrenal insufficiency is the maintenance of the patient in good health by means of the proper combination of sodium chloride therapy, low potassium diet.

oil in which it is dissolved is an uncommon difficulty easily avoided by the use of another solvent. *Edema* may follow overdosage of this hormone especially if large amounts of salt are given with it. This demands a reduction of the dose of salt or of hormone, but if both are reduced together crisis may be precipitated. Some increase in the size of the heart is the rule in response to treatment which increases blood volume. Cardiac distress and occasionally pulmonary edema may occur particularly in the presence of preëxisting heart disease. *Hypertension* may develop and is controlled by adjusting the dose of hormone or sodium chloride. It is possible to produce a low serum potassium and *muscular weakness* from desoxycorticosterone and the potassium intake should not be restricted when this drug is given. *Hypoglycemia* is not prevented by treatment with desoxycorticosterone alone. It is especially likely to occur when acute infections or gastro-intestinal disturbances increase the requirement or interfere with the intake of carbohydrate.

#### ADRENAL CORTICAL TUMORS AND RELATED DISORDERS

The clinical signs of hyperplasia or hyperfunction of the adrenal cortex vary widely. There are *adenomas* which produce no endocrine symptoms and which are only discovered as incidental findings at autopsy. The *adrenogenital syndrome* or *adrenal virilism* is a disorder of the sex characteristics consisting of the following abnormalities: In children there is male or female sexual precocity, a rare condition as only forty cases in girls and seventeen in boys have been reported.<sup>4</sup> In young women there are hirsutism of varying degree, amenorrhea, deepening of the voice, enlargement of the clitoris, acne and masculine bodily contour and musculature. Finally there is the extensive disturbance of metabolism seen in *Cushing's syndrome*. Although its pathogenesis is not fully understood, this condition has been included in Table 1, subject to question, because there is adrenal hyperplasia or tumor regardless of whether or not there is a tumor of some other endocrine gland. Between these distinct entities an endless variety of symptom-complexes are met



TABLE 2  
TREATMENT OF ADRENAL CRISIS  
(Condensed from Thorn<sup>2</sup>)

Day	Medication
1st	Warm Bed 1000 cc. 1.5% NaCl 1000 cc. 5% glucose 25 cc. adrenal cortical extract } Intravenously: Begun at once. 0.5 cc. epinephrine subcutaneously—if blood pressure below 70. 25 cc. cortical extract subcutaneously (acts 2-6 hours). 25 mg. desoxycorticosterone acetate in oil intramuscularly in divided doses (acts 24 hours). In second 12 hours: 500-1000 cc. normal saline 500-1000 cc. 5% glucose } Intravenously
2nd	5 cc. cortical extract every 4 to 6 hours. 15 mg. desoxycorticosterone acetate in oil—single intramuscular injection. 1000 cc. normal saline 1000 cc. 5% glucose } Intravenously. Begin liquid diet; if not tolerated repeat intravenous saline and glucose.
3rd	5 cc. cortical extract twice during day. 10 mg. desoxycorticosterone acetate in oil. If fluids and soft diet not tolerated, repeat intravenous infusions of glucose and saline.
4th	3 to 6 gm. sodium chloride (1 gm. enteric-coated tablets) by mouth. 10 gm. desoxycorticosterone acetate in oil.
5th	6 gm. sodium chloride daily. 2-5 gm. desoxycorticosterone acetate in oil daily as required to maintain body weight.

If at any time edema appears, reduce the amount of salt or desoxycorticosterone acetate. If hypoglycemia occurs during convalescence resume cortical extract 5-10 cc. every 4 to 6 hours.

intestinal irritation from large doses or an increase in the severity of the disease commonly leads to anorexia, nausea and vomiting before edema appears. No symptoms of overdosage have been observed from cortical extract. According to Thorn and associates<sup>11</sup> this is because extract contains a normal proportion, or balanced composition, of steroids which cause not only the retention of sodium but also the excretion of sodium, as well as regulation of metabolism.

When desoxycorticosterone is used, a number of complications may be encountered. A *local reaction* to the sesame

Tumor	Clinical	Röntgenologic	Roentgen studies clinically indicated, urinary excretion, and <i>W. &amp; W.</i> by chemical methods
General Symptoms and Pathology	<p><b>Virilism</b></p> <p><b>Cushing's Syndrome</b></p>	<p>None seen (under 21)</p> <p>Increases of bone density</p> <p>Osteoporosis</p> <p>Articular changes</p> <p>Metastases</p>	<p>Roentgen studies clinically indicated, urinary excretion, and <i>W. &amp; W.</i> by chemical methods</p>
Adrenal Cortical Tumor or Hyperplasia	<p><b>A. Wilms</b></p> <p>Sexual precocity in boys</p> <p>Virilism or precocity in girls</p> <p>Growth retardation at first, then retarded</p> <p>Amenorrhea (with virilism)</p> <p><b>B. Cushing's syndrome</b></p> <p>All classical symptoms</p> <p>Weakness</p> <p>Visual fields normal</p> <p><b>C. Nonfunctioning tumors</b></p> <p>If benign, are undiagnosed</p> <p>If malignant, have symptoms of tumor</p> <p>Hematuria</p> <p>Metastases especially to lungs</p>	<p>Chest for metastases</p> <p>Prenatal roentgenogram (virilism)</p> <p>Osteoporosis (with Cushing's syndrome)</p> <p>Urogram</p> <p>Vertebral air injection</p> <p>Body section roentgenography</p> <p>Efficient three procedures in combination advised by roentgenologist</p> <p>Pathology found normal</p>	<p>Androgens and 17-K<sub>17</sub> greatly increased, Estrogens increased by some methods</p> <p>Glucose tolerance test</p> <p>Renal function tests (hypernatremia)</p> <p>Androgens increased</p> <p>17-K<sub>17</sub> increased</p> <p>Hematuria</p> <p>Hormones not studied</p>
Phenochrom and Paraganglioma	<p>Usually in children</p> <p>Sexual precocity</p> <p>Neurological signs</p> <p>Papillothyma</p> <p>Increases of intracranial pressure</p> <p>Visual fields</p>	<p>Signs of increased intracranial pressure</p> <p>Possible increased calcification and displacement of pituitary gland</p> <p>Vertebral roentgenogram</p> <p>Pituitary fossa—often enlarged</p>	<p>Androgens increased (M)</p> <p>Estrogens increased (B)</p> <p>17-K<sub>17</sub> normal</p>
Benign Adenoma of Pituitary (Cushing's Disease)	<p>Cushing's syndrome</p> <p>Visual fields usually normal</p>	<p>Pituitary fossa normal</p> <p>Osteoporosis</p> <p>Arteriosclerosis</p> <p>Therapeutic test of irradiation</p>	<p>Glucose tolerance test</p> <p>Renal function tests</p> <p>Androgens increased</p> <p>17-K<sub>17</sub> increased</p>
Thyroid Carcinoma	<p>Cushing's syndrome</p> <p>Increased mediastinal dullness</p>	<p>Like Cushing's syndrome</p> <p>Mediastinal enlargement</p>	<p>Like Cushing's syndrome (above)</p>
Adrenocortical Carcinoma	<p>Pelvic examination</p> <p>Pelvic exploration</p>	<p>Metastases</p> <p>When Cushing's syndrome occurs retroperitoneal, etc.</p>	<p>17-K<sub>17</sub> normal</p> <p>(Presumably increased if Cushing's syndrome present.)</p>

\* Hormone assays are not widely available but are an active field of investigation.

† Only 4 cases reported. Cushing's syndrome without Cushing's syndrome are without endocrine symptoms.

which cannot be explained by morbid anatomical changes. Thus, the obese, slightly hirsute, hypertensive woman who develops diabetes after the menopause (amenorrhea) presents many of the abnormalities included in the rare syndrome of Cushing. Sometimes it requires the physician's best judgment to save these people from time-consuming endocrine studies; sometimes it takes all of his acuity to diagnose the uncommon endocrine disorder. From the literature and from his experience the writer has arranged the differential diagnosis of adrenal cortical tumors in outline form. This is done in Table 3 concerning which the following facts should be noted.

Cushing's syndrome is distinguished from Cushing's disease which is the syndrome associated with basophile adenoma of the pituitary gland. The symptoms of adrenal hyperfunction of all types are based on the analysis of fifty-five proved cases by Lukens, Flippin and Thigpen.<sup>17</sup> Minor symptoms and findings have been excluded and the reader will be aware of this abbreviation. The writer is indebted to Dr. E. P. Pendergrass for recommending the roentgenologic procedures that are most helpful. Finally all of the investigations listed in Table 3 do not have to be carried out in order to decide on the course of action in a single patient. This is illustrated by the abstracts of two case histories.

CASE I.—An eighteen-year-old girl who had developed hirsutism four years previously was admitted with extreme virilism. She had never menstruated, had only masculine breasts, and all the other signs of virilism. Roentgenograms of the skull and chest were normal; that of the pelvis showed complete union of epiphyses indicating a bone age of twenty-one years or more. Perirenal air injection combined with body section roentgenography gave no definite evidence of adrenal enlargement. Nevertheless, her symptoms were so distressing that she agreed to exploration of the adrenals. Bilateral hyperplasia of the adrenals was found, and except for biopsy no resection of the glands was attempted. At a previous pelvic laparotomy atresia of the ovaries had been found so that, after the exclusion of adrenal tumor, gonadotropic therapy was recommended but the patient could not be followed to ascertain whether this was done.

CASE II.—A woman, aged thirty years, was admitted to the hospital with the fully developed picture of Cushing's syndrome, including the pathognomonic striae, of three months' duration. Roentgenograms of the skull showed a normal sella and demineralization of the bone. Pelvic examination was negative excluding gross ovarian tumor. Roentgenograms

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of the chest revealed multiple metastatic nodules in the lungs. This early extensive pulmonary metastasis pointed to a malignant adrenal tumor as the cause of the endocrinopathy. No further studies were attempted and the diagnosis was confirmed at autopsy three months later.

### Treatment of Adrenal Tumor

The treatment of adrenal tumor is *surgical removal* if metastasis has not taken place. Brilliant results have followed the excision of adenomas causing adrenal virilism. No such recoveries have been reported for Cushing's syndrome, and the surgical treatment of adrenal hyperplasia remains unsatisfactory although a few instances of some improvement following partial adrenalectomy have been recorded. The hazards of adrenal surgery have been pointed out by several clinics.<sup>4, 18</sup>

*Pituitary irradiation* has been of value in some cases of Cushing's disease and should always be given a trial when the syndrome is present. All too frequently it fails to cause improvement.

With virilism, atresia of the ovaries has frequently been found, and when there is no adrenal tumor gonadotropic *hormone therapy* would seem worth a trial. Unfortunately there is no potent pituitary gonadotropin available; that from mare's serum is untried, and the gonadotropins from pregnancy urine have not proved beneficial. The conflicting reports on *estrogenic treatment* permit no conclusion. *Testosterone* has been used in Cushing's syndrome with benefit in some cases and failure in others.

In conclusion, it appears that the treatment of adrenal hyperfunction is surgical or palliative, the latter being directed by the physician's ingenuity and judgment.

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## DIAGNOSIS AND TREATMENT OF OVARIAN TUMORS PRESENTING ENDOCRINE MANIFESTATIONS\*

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WHEN one considers the basic pathologic conditions of the ovary that may be responsible for certain pelvic and general symptoms it is essential to determine as soon as possible whether or not the enlargement is non-neoplastic (physiologic) or neoplastic in character. This is not always easy, but the problem is somewhat simplified by remembering at the outset that ovarian neoplasms presenting endocrine manifestations are far less common than are ovarian enlargements or abnormalities associated with functional or organic disturbances. With this general premise in mind, we can first discuss the diagnosis in a general way, emphasizing later the detailed points of differentiation and the variation in treatment with respect to the groups mentioned.

### DIAGNOSIS

Undoubtedly ovarian enlargements, varying in character and size, are present many times without giving rise to any symptomatology whatsoever. This is particularly true of those that may be regarded as functional or physiologic, but it is also true that such lesions may present a very definite train of symptoms under the varying conditions of their occurrence. On the other hand, while neoplastic growths may fail to produce any disturbance for some time, sooner or later their presence will provoke attention. Annoyance to the patient usually invites investigation, but the ovarian abnormality, regardless of its character, may be discovered accidentally in the course of a routine physical examination.

In any event it is of primary importance to secure a con-

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The former may be single or multiple in type, while the latter are solitary.

A single graafian follicle cyst is sometimes spoken of as *hydrops folliculi*. It varies in size, is thin walled and projects from the surface of the ovary. The content is serous or sero-sanguineous and grossly it may be difficult to tell whether or not it is a maturing graafian follicle, a cystic corpus luteum or a persistent abnormality resulting from either. Again we may find multiple small cysts present, so-called *retention cysts*, resulting perhaps from follicular atresia, and the designation *cystic degeneration of the ovary* may well be applied to such a lesion, compatible too with the frequently used term, *polycystic ovary*. Fibrosis of the cortex may accompany these cystic changes. Inflammatory changes incident to pelvic infection, congestion associated with uterine displacements or ovarian prolapse, and hormonal dysfunction, either alone or in combination, are the factors probably responsible for, or an accompaniment of, the development of these non-neoplastic tumors. Unfortunately, they cannot always be clearly differentiated, no matter how carefully one considers all the attending circumstances.

The symptoms complained of are to some extent dependent upon the predominant stimulus, and the diagnosis rests upon their interpretation combined with the physical findings. For that reason it might be well to describe typical clinical types that may be encountered, with accompanying comment relative to treatment, emphasizing particularly those instances in which associated endocrine manifestations of a functional nature occur. In general, such patients with cystic ovarian changes fall into one of the two groups:

1. Those in whom excessive or irregular uterine bleeding occurs, with or without associated lower abdominal pain of varying character. Such symptoms usually occur in the second and third decades of life, but they may also be present in women of menopausal age.

2. Those in whom amenorrhea or scanty menstruation, with or without pelvic distress, are the principal complaints. Younger women are almost invariably the ones who are affected.



cise, accurate *history*. Since some aberration of menstruation, accompanied by pelvic distress of varying character, is the symptom most often complained of, it is essential to know particularly when the menarche was established, what has been the subsequent menstrual habit of the individual, when any alteration has occurred, and its possible relation to pregnancy. Pain, of course, may be either a manifestation of the abnormality itself or it may be the result of, or dependent upon an associated pelvic disorder. Hence the relation of pain to the menstrual cycle, or its independence of the latter, together with the character of the distress, must be carefully ascertained. Symptoms apart from the pelvis may likewise have a definite bearing on the diagnosis.

*Examination* must not be limited to the pelvis. Very often important clues are revealed by a meticulous survey of the entire body. Basing a diagnosis on a single examination, particularly of the pelvis, is unwise, for repetition of the initial consultation may be very revealing and avoid the embarrassment that sometimes results from a "snap" diagnosis. A post-menstrual examination, for instance, may yield quite different information from that secured immediately before the flow has begun. Remember, too, that the bowels and bladder should be well emptied prior to bimanual palpation of the pelvic organs. Accurate examination is truly essential in differentiating organic disease from functional manifestations.

*Laboratory tests* are not always essential, but the simpler ones, such as urinalysis, blood count and a basal metabolic estimation, are often helpful. Puzzling cases will demand more intricate study, including x-rays, hormonal determinations of blood and urine, and diagnostic curettage. In most instances, however, these more elaborate procedures are not needed, but should they be indicated the patient can usually be sent to an institution where these means of investigation are more readily accessible.

#### NON-NEOPLASTIC TUMORS

Cystic enlargements of the ovary may occur as the result of physiologic abnormality incident to the development or retrocession of the graafian follicle or the corpus luteum.

When the patient is a young child or virginal adolescent, the vagina and cervix can be competently observed through a Kelly cystoscope of relatively small caliber, and an accompanying bimanual rectal examination will generally suffice to determine the status of the fundus and adnexa. In older patients the problem is less difficult, and organic disease can be excluded rather readily if one is thorough in his approach.

The important finding is that of an *ovarian enlargement*. This may be unilateral or bilateral. The difficulty, of course, is to decide whether the cystically enlarged ovary represents a new growth or whether it is merely representative of a physiologic misdemeanor. In the latter instance the enlargement is not exceptional, the ovary usually being no larger than a lime or an average-sized lemon. It is freely movable, unless adherent because of organic disease, or perhaps it is prolapsed. Sensitivity generally accompanies palpation. A neoplastic enlargement, on the other hand, is more likely to be larger and persists. Repetition of the examination during a period of observation is most helpful in determining the true nature of the lesion, for the follicle cyst changes in size from time to time, a property not exhibited by neoplasms.

Having determined to the best of one's ability that the cyst is not a true new growth, the basic principle of treatment should be *expectancy*, for the symptomatology presented may not necessarily be the result of the follicle cyst. In rare instances the manipulation incident to the examination might result in altering the character of the follicle cyst, perhaps causing it to rupture, and the menstrual cycle, if disturbed, may again become properly spaced. If any accompanying bleeding is not excessive, and the general condition has not been appreciably affected, reassurance alone may be excellent therapy. This is particularly true of those cases occurring at puberty, resulting very often from varying degrees of endometrial hyperplasia, which in itself is usually self-limited as complete feminine development is approached.

Naturally anemia and fatigue must be appropriately treated with ferruginous tonics, adequate rest and diet, fortified with appropriate vitamin therapy if indicated. In the more severe cases where the presence of the cystic ovary is thought to

These clinical groups will now be discussed in proper sequence, with the avoidance of unnecessary repetition.

#### 1. NON-NEOPLASTIC CYSTS ASSOCIATED WITH EXCESSIVE OR IRREGULAR UTERINE BLEEDING

Most frequently patients with this type of tumor, usually a *follicle cyst*, are either adolescent girls or younger women in the twenties. The latter may be single, or if married pregnancy may not have occurred. On the other hand, patients with such symptoms may be in the menopausal epoch. Prior to the initiation of their complaint, the menstrual periods may have been quite regular and normal in amount, but more often irregularities of minor degree have been noted. The onset of menstruation may have been relatively late, and usually some degree of dysmenorrhea has been present. Not infrequently a mucoid vaginal discharge may also have occurred as the result of a congenital eversion and erosion of the cervical mucosa.

The bleeding may be in the nature of a well-defined menorrhagia, or it might be a long-drawn-out affair having followed a period of amenorrhea, as is so often seen in endometrial hyperplasia. In some instances periods of prolonged bleeding can follow one another with but short intervals of respite. Dysmenorrhea may be present, either combined with or independent of pelvic distress, varying in character, location and relation to menstruation or irregular bleeding.

Interval headaches, gastro-intestinal disturbances, and either diarrhea or constipation may accompany the condition.

*Examination* should be directed primarily toward the discovery of abnormal constitutional factors. Any deviation from the normal weight should be noted, and the presence or absence of fever ascertained. A systematic survey with particular attention to the condition of the thyroid, heart and lungs for evidence of abnormality is essential. If anemia is evident or suspected, a blood count should not be neglected. with blood pressure and urinalysis as a matter of record.

*Pelvic examination* must be thorough, beginning with inspection of the external genitalia, visualization of the vagina and cervix and bimanual palpation of the fundus and adnexa.

functional bleeding or it may be independent of it; it could occur at the time of the bleeding or be present during intervals of freedom from it. The latter phenomenon is not uncommonly complained of by patients who have perfectly regular and normal periods, in which event it is often spoken of as "mittelschmerz." Rarely a bloody discharge accompanies it. The explanation of this phenomenon is not clear. Here again, rest and reassurance, with mild sedative prescriptions relieve most patients promptly unless an organic condition has been overlooked. Hot saline therapeutic douches are comforting (a teaspoonful of salt to 2 quarts of hot water, repeated three or four times over a period of an hour, and administered in the recumbent position). If a reasonable trial of these palliative measures is not successful, one had better look again for an undiscovered organic cause—pelvic inflammation, endometriosis, or neoplasm, rather than to persist in the diagnosis of cystic ovary. Sometimes a uterine retrodisplacement, with accompanying ovarian prolapse and cystic changes, resulting in subsequent circulatory derangement has not been given sufficient consideration, and its proper correction may ultimately relieve the patient. In the married, nulliparous woman, such a situation may likewise be responsible for dyspareunia and sterility, requiring eventual operative interference. One must always bear in mind the possibility of spontaneous rupture of a follicle cyst with accompanying intra-abdominal bleeding. It is not rare to have hemorrhage of sufficient magnitude to necessitate surgical intervention, and usually such a decision is made because a ruptured tubal pregnancy or tubal abortion is suspected.

## 2. NON-NEOPLASTIC CYSTS ASSOCIATED WITH ABSENT OR SCANTY MENSTRUATION

Existing much less commonly is the association of a cystic ovary with absent or scanty menstruation. This syndrome is in definite contrast with that just mentioned in relation to follicle cysts, for here we have a cystic or persistent corpus luteum as the probable causative factor. As previously stated, these *corpus luteum* cysts may be difficult to differentiate from a maturing graafian follicle cyst. They vary in size, appear as elevations on the cortex of the ovary, but are more often yellowish in color with a rather irregular membrane. A young woman, who previously exhibited normal menstrual function, may gradually note longer intervals between her periods, and the latter may become more scanty in addition until cessation finally occurs. On the other hand, amenorrhea may develop rather suddenly. Frequently, there is accompanying soreness of the breasts, and pelvic distress of varying character may be complained of, but generally to a lesser degree than is the case with follicle cysts. Sterility is a frequent problem in this group of patients.

be associated with functional uterine bleeding of some magnitude, blood transfusion should not be ignored and curettage may be helpful for a while at least.

*Hormonal therapy* is likely to prove disappointing, as it is by no means standard in its therapeutic application. One can employ these preparations in adolescents and younger women when a self-limited effect seems lacking, before resorting to curettage. Any major surgical procedure such as ovarian resection or oophorectomy, for purely functional bleeding and irradiation as well, should most certainly be avoided in the younger age groups. Meddlesome surgery for an uncomplicated, purely cystic ovary or ovaries will almost always prove ineffective and is very likely to be followed by continuance or recurrence of the symptoms previously complained of. *Chorionic gonadotropins*, 100 to 500 units daily may be used hypodermically in an attempt to limit the bleeding. *Progesterone*, 1 to 5 mg. daily has also been suggested. *Testosterone propionate*, 10 to 25 mg., two to three times weekly is also employed, but the tendency toward masculinization, especially with larger dosage makes it less desirable. *Thyroid extract*, carefully controlled, in a dosage of  $\frac{1}{2}$  to 1 grain daily is helpful in some instances, but its use had better be checked with basal metabolic estimations. *Lugol's solution*, 1 to 5 minims three times daily, may also be tried with caution in some instances.

When, however, we are dealing with older patients, especially with those of menopausal age, it is far better to employ either surgery or irradiation with radium to control abnormal bleeding symptoms that are thought to be associated with the cystic ovary. *Hormonal therapy has no necessary or secure application in the abnormal bleeding of menopausal women, for its use may mask the presence of undiscovered malignancy.* Preservation of the child-bearing function no longer dictates conservation and surgery or radium can be resorted to as indicated with reasonable prospects of success.

*Control of Pain.*—Pain may accompany the cystic ovary, either as dysmenorrhea or as an intermittent pelvic distress, unilateral or bilateral in character. Too often pain is diagnosed as "chronic appendicitis" and an unnecessary appendectomy follows, accompanied not infrequently with destructive ovarian surgery. Discomfort of this sort can be associated with

duce. The recognition of this type of cyst is dependent upon the diagnosis of such relatively rare uterine lesions. The regression of cysts of this character depends upon the response of the primary neoplasm to indicated treatment. It is only metastatic spread to the ovaries in a patient with chorionepithelioma that places these structures within the realm of neoplastic tumors.

### NEOPLASTIC TUMORS

We now approach a discussion of true neoplastic tumors of the ovary associated with endocrine manifestations. In general, most ovarian new growths are not accompanied by so significant a syndrome. Whether benign or malignant, cystic or solid, it is usually enlargement of the abdomen, with associated pain and gastro-intestinal symptoms that makes the patient conscious of an abdominal or pelvic abnormality. Menstrual disturbances, or irregular uterine bleeding, are apt to be lacking except in the presence of complicating pelvic disease.

It has already been stated that the most difficult matter is to decide whether or not the ovarian enlargement present is neoplastic, and the way in which such a decision can usually be reached has likewise been stressed. When the history and an adequate examination convince one that the enlargement is neoplastic and not physiologic or functional, it is well to remember which varieties of the former are more commonly encountered. With this thought in mind, we may first mention *adenocystoma* (or *cystadenoma*), pseudomucinous or serous, and simple or papillary in character. *Endometrial cysts* (so-called "chocolate cysts") are rather commonly observed, sometimes as part and parcel of a diffuse pelvic endometriosis. Next we meet with *carcinoma* of various patterns, and less frequently with *teratoma* (cystic and solid), *fibroma* and *sarcoma*. While it cannot be denied that unusual endocrine manifestations may sometimes be associated with the neoplasms mentioned, it is entirely possible that such a finding may be coincidental except in certain rare instances, as may occasionally occur with teratoma and sarcoma. Occasionally a teratoma may contain sufficient thyroid tissue to give rise to hyperthyroidism; sarcomata have been known to produce abnormal endocrine manifestations in infants and young girls.

Symptoms of this sort generally result in rather prompt examination, and the detection of the ovarian enlargement. The possibility of ectopic gestation may be so strongly considered that immediate laparotomy is deemed advisable. If such a procedure is carried out in a doubtful case, very careful surgical judgment is essential when the pelvis is exposed and no ectopic gestation is found. The ovarian enlargement might be a cystic corpus luteum, the removal of which would terminate an early intra-uterine pregnancy, while resection of a corpus luteum cyst, to the contrary, might well have a beneficial effect.

Often, however, the discovery of a possible corpus luteum cyst will permit of further observation and study. The biologic test for pregnancy and the blood count are obviously helpful. Evaluation of possible constitutional and endocrine disturbance is essential, for not infrequently hypothyroidism of varying degree, with or without associated obesity, is the source of trouble which might be blamed on a possible corpus luteum or follicle cyst. In an event of this sort surgery would be ill-advised, and carefully regulated *thyroid therapy* with general measures might be productive of better results. Again we must not forget that self-limitation may be the answer to the difficulty. *Estrogenic hormonal therapy*, both natural and synthetic, is purely substitutional in character and the use of gonadotropic preparations for activation has given rise to numerous controversial and contradictory reports, as has recommended x-ray therapy. *Surgery* is only justifiable after a relatively long period of observation, with thoughtful consideration of the age of the patient, the problem of fertility and the possibility that the ovarian enlargement is neoplastic. If and when operative interference is decided upon, it should be limited to excision of the cyst, if a new growth can be excluded, and the patient should be made aware of the fact that a similar condition might conceivably arise again at a later date.

For completeness, attention should be called to the occurrence of the so-called *compound theca lutein cysts* of the ovary that are associated with hydatiform mole and chorionepithelioma. The physiologic development of these cystic ovarian enlargements is dependent upon the enormous production of chorionic gonadotropic hormone that these tumors pro-

duce. The recognition of this type of cyst is dependent upon the diagnosis of such relatively rare uterine lesions. The regression of cysts of this character depends upon the response of the primary neoplasm to indicated treatment. It is only metastatic spread to the ovaries in a patient with chorionepithelioma that places these structures within the realm of neoplastic tumors.

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Nevertheless, it is quite true that the majority of patients exhibiting any of the varieties of ovarian new growths that have been noted, generally present no particular evidence of unusual endocrine change.

Let us then turn our attention to that relatively small group of tumors that are responsible for exceptionally striking endocrinopathies. What are they, when do they occur, when should they be suspected and how should they be treated? Roughly speaking, two groups are recognized—those producing feminizing, and those producing masculinizing symptoms. The former are more frequent than the latter.

#### 1. OVARIAN TUMORS PRODUCING FEMINIZING SYMPTOMS

Most commonly occurring in this group are the *granulosa cell tumors*, which are believed to arise from the granulosa cell rests that remain after the development of the follicular epithelium that surrounds the ova to make up the primordial follicles. Another view held is that their primary origin is from the progranulosa mesenchyme. If this is true it can well account for the origin of a *thecoma* or a *luteoma*, neoplasms closely allied with granulosa cell tumors. Microscopically, granulosa cell tumors vary in architecture, but the predominant feature is one of pseudo-ovogenesis, simulating in appearance groups of primitive follicles. The thecoma presents a substantial addition of connective tissue to its structure, while the luteoma represents varying degrees of luteinization occurring either in a granulosa cell tumor or in a thecoma. Naturally the histogenic interpretations relating to thecoma and luteoma have provoked controversy regarding their differentiation, but for clinical purposes we need only consider them essentially as being within the category of granulosa cell tumors.

These tumors vary in size and consistency as do other ovarian neoplasms; often they present a yellowish appearance when bisected. Because of their origin they are able to manufacture an appreciable quantity of estrogenic hormone. This property is the basis of the symptomatology for which they are not infrequently responsible. They are potentially malignant, perhaps frankly so in about a third of the cases, and for

that reason they should be so regarded if an immediate diagnosis can be made. This is not usually possible, however, for on examination one cannot differentiate them by palpation from any other ovarian neoplasm. Their true character may not even be recognized grossly at operation, and the diagnosis is made in the laboratory.

Granulosa cell tumors may appear at any age. When discovered during the normal reproductive period there is little in the symptomatology to distinguish them from other ovarian new growths, as has been stated. The hormonal content that they possess can add little to the same effects that hyperestrogenism can produce in the case of the follicle cysts so closely related to functional uterine bleeding or polyhormonal amenorrhea.

On the other hand, there is a sound reason to suspect the presence of a granulosa cell tumor when an infant or young girl presents definite evidence of precocity—*prepubertal uterine bleeding, development of pubic and axillary hair and unusual enlargements of the breasts*. Such a syndrome should always challenge one to make a careful pelvic examination, that will not only exclude an unusually early malignancy of the cervix or vagina, but may result in the discovery of an ovarian tumor, perhaps associated with an enlarged uterus. With such symptomatology and findings present, there is no place for expectant treatment, either with medicines, irradiation therapy, or hormonal injections. Prompt surgery is indicated, with the removal of the tumor which is usually solitary. It is not necessary to sacrifice the uterus or an apparently normal ovary on the opposite side. If no metastasis is demonstrable, recovery is very apt to occur with subsequent regression of the precocious manifestations.

The possible presence of a granulosa cell tumor should always be thought of in the presence of *postmenopausal bleeding*. More frequently this symptom is associated with uterine malignancy, particularly of the fundus, or it may be the result of benign processes. Diagnostic curettage can usually be relied upon to settle such points. If the curettage is negative, or if it reveals endometrial hyperplasia in company with a definitely palpable ovarian tumor, it is well to

plan an exploratory laparotomy on the assumption that a granulosa cell tumor might be present. Very occasionally an unsuspected carcinoma of the tube may be found. Again the establishment of periodic menstruation some time after the menopause has occurred may result in the discovery of a palpable ovarian tumor following investigation of so strange a phenomenon, and the answer may then be found at operation. The revival of estrogenic function due to the development of the tumor following the menopause is responsible for initiation of menstrual-like bleeding, but would probably contribute little in the way of alteration of any secondary sex characteristics which might naturally have undergone previous menopausal regression.

*Surgery* in the case of women in the reproductive and postmenopausal epochs who have developed granulosa cell tumors would necessarily be of a more radical nature and be governed by the exact pathologic condition encountered. Removal of the tumor in the absence of metastases should result in the subsidence of symptoms and complete cure in the majority of instances, for the tumors are of relatively low-grade malignancy, but a systematic follow-up is essential. A warning is again sounded against the use of hormonal therapy in an attempt to control postmenopausal bleeding, because by so doing, organic lesions are apt to be overlooked. More radical measures are really conservative in that organic disease is eradicated and the life span of the patient thereby prolonged.

## 2. OVARIAN TUMORS PRODUCING MASCULINIZING SYMPTOMS

Most commonly seen among this rarer group of tumors is the *arrhenoblastoma*. This neoplasm is believed to arise from cellular elements present in the indifferent stage of the sexual gland before the gonad becomes fully determined either as a testicle or as an ovary. Such potential testicular rests in the ovary may develop later on and produce androgenic hormone, thus being responsible for the appearance of masculine characteristics in youth or adult life. Histologically three forms have been observed: (1) a well-differentiated type, in which testicular tubules are readily recognizable; (2) a less exact

form; (3) a very indefinite, undifferentiated variety. A single tumor may even reveal a composite structure.

This type of ovarian neoplasm gives rise to such striking endocrine manifestations that observance of the syndrome alone would lead at once to a careful general and pelvic examination. Such tumors are relatively moderate in size and are usually of a solid consistency, but cystic change may be present in some areas. Generally they are grayish-yellow in color when observed in situ, and are said to be of comparatively low malignancy.

Usually these tumors have occurred in younger patients, relatively few having been reported after the initiation of the menopause. The possibility of an arrhenoblastoma being present should be borne in mind when a developing amenorrhea is accompanied with breast atrophy and loss of fatty tissue over the body. Pelvic examination at this time may reveal no appreciable ovarian or uterine change, and repeated observations are certainly in order. If the physical status of the patient remains relatively stationary, we may be dealing with arrested genital development, or thyroid or pituitary disturbance of varying degree. Contrariwise, definite evidence of masculinization may now set in—*pronounced hirsutism, hypertrophy of the clitoris and even a distinct change from the female type of voice to a male type*. Should these changes occur, an ovarian tumor and a uterus smaller than normal might be discovered by palpation.

This is the description of a typical patient in whom an arrhenoblastoma has been the provocative factor. Naturally, the symptoms mentioned may be much less pronounced, as is sometimes seen in the hypotonic constitutional type of woman who exhibits masculine or intersexual characteristics and for which an underlying endocrinopathy may be responsible. When encountering a woman of this type, even well-chosen general measures of therapy, including the administration of endocrine preparations, may result in overlooking a masculinizing ovarian neoplasm if one is not alert to such a possibility. Proceeding in a similar vein of thought, it must not be forgotten that tumors or hyperplasia of the adrenal

cortex and pituitary basophilism may be responsible for different degrees of masculinization.

Once the diagnosis is reasonably certain, or even strongly suspected, *surgery* should be recommended and it should be of a conservative nature, for removal of this unusual ovarian growth is very likely to be followed by the disappearance of the masculinity that has been described, and be followed by the restoration of feminine attributes. The patient thus treated should be observed consistently afterward, for recurrence is possible though not probable. Apart from this reason is the unique interest that so rare a condition excites.

Adrenal-like cell tumors of the ovary have been referred to as *adrenal adenomas of the ovary*, and also as *masculinovoblastoma*. They represent an extremely rare type of ovarian neoplasm in which aberrant adrenal tissue, similar to that seen in the adrenal cortex, predominates. Their occurrence is really mentioned for completeness of discussion. Dispute has arisen regarding their differentiation from the luteoma. Of practical value is the fact that their rare occurrence is apt to produce the same signs and symptoms that occur with arrhenoblastoma, the details of which need not be rehearsed.

#### SUMMARY

1. Non-neoplastic enlargements of the ovary are either in the nature of follicle or corpus luteum cysts. They represent a physiologic alteration that may or may not give rise to functional disturbance of an endocrine nature. Treatment is rarely surgical unless complicating pelvic disease requires operative interference.

2. On the other hand, certain neoplastic enlargements of the ovary present striking endocrine manifestations, either of a feminizing or masculinizing nature. The former are the granulosa cell and allied tumors, and the latter include arrhenoblastoma and adrenal-like growths. Treatment in these instances is entirely surgical.

## DIAGNOSIS AND TREATMENT OF AMENORRHEA\*

S. LEON ISRAEL, M.D., F.A.C.S.†

It is impossible to consider in a single paper our present knowledge of menstrual disorders, a field which encompasses an enormous section of medical knowledge and theory. For that reason, amenorrhea alone will be discussed and aberrations of menstrual function which may be ascribed to organic causes, such as the amenorrhea of hypophyseal tumors or of ovarian arrhenoblastoma, are not included in this presentation. This review deals with the cessations of the menstrual cycle which are loosely termed "of endocrine origin," and which present themselves as either oligomenorrhea or amenorrhea.

### The Normal Menstrual Cycle

Menstruation includes both anabolic and catabolic processes which occur periodically in the ovary and uterus simultaneously. Despite the fact that most physicians have some understanding of the current conception of normal menstruation, it is essential to review briefly the cardinal principles of menstrual physiology before discussing any pathologic variety. The cyclic ovarian changes are governed solely by the secretions of the anterior hypophysis. The latter produces two gonadotropic hormones which are responsible for follicle maturation and corpus luteum formation, respectively, in the ovary. In turn, each of these two phases of the ovarian cycle controls a portion of the uterine cycle. The cyclic changes in the endometrium are entirely dependent upon the hormones secreted by the ovarian follicles and the corpus luteum. The periodic, postmenstrual ripening of a group of ovarian primordial follicles is productive of *estrogen*, the hormone which effects the proliferative phase in the endometrium.

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During the first half of the menstrual cycle, as a result of the ovarian follicular hormone, estrogen, the endometrium changes from a thin layer of cells practically devoid of glands to a tall, richly glandular tissue. At approximately the mid-interval of the cycle, one of the growing ovarian follicles matures, ovulation occurs, and the collapsed follicle is transformed within a few days into a corpus luteum. This change in the ovary is effected by the gonadotropic hormones of the anterior hypophysis. The luteinizing gonadotropin supports the continued function of the corpus luteum. The lutein cells continue, as their forebears in the follicle did, to produce estrogen but, in addition, also secrete *progesterin*, the characteristic principle of the corpus luteum.

During the second half of the cycle, progesterin causes the estrogen-primed endometrium to become a hyperemic, highly functional tissue richly endowed with nutritive substances required for the embedment and support of a fertilized ovum. If a fertilized ovum does not eventuate, the corpus luteum disintegrates and, almost immediately thereafter, the endometrium so earnestly constructed in anticipation of pregnancy is dismantled by the process of menstruation.

There are several interesting gaps in the brief summary of the menstrual cycle stated in the previous paragraph. For instance, it cannot be stated with accuracy what precisely initiates the mechanism of the menstrual flow, although an anatomic description has been carefully delineated (Daron,<sup>1</sup> Bartelmez<sup>2</sup> and Markee<sup>3</sup>). It is also important for therapeutic purposes to remember that there are at least two substances, mare serum gonadotropin and pregnancy urine gonadotropin, which are capable of evoking some, but not all, of the actions of the gonadotropic principles of the anterior hypophysis. It is, moreover, essential for the physician to recall certain therapeutic precepts concerning the management of amenorrhea of endocrine origin.

#### Therapeutic Principles

The following maxims should be borne in mind, as well as the mechanism of the normal menstrual cycle, when faced with the problem of amenorrhea.

1. *Elimination of Organic and Constitutional Disease.*—There is no difference between the amenorrhea of dysfunctional origin and that caused by either an organic pelvic disorder or a constitutional ailment. The differential diagnosis must carefully exclude the presence of all possible organic lesions and systemic diseases before the amenorrhea may be ascribed to a simple alteration of function. This requires the use of all of the diagnostic procedures available, including complete physical examination, blood count, urinalysis, serologic study, and determination of the basal metabolic rate. It is occasionally necessary, even for the experienced gynecologist, to resort to the use of a biologic pregnancy test in order to be certain that pregnancy is not the cause of the amenorrhea. *It is imperative to remember that a woman may conceive during the course of amenorrhea.* Thus, the finding of an enlarged uterus, suggesting an early pregnancy, in a woman who had not menstruated for six months must not be ignored. If the pregnancy test in such an instance is positive, it must be assumed that the patient would have completed a menstrual cycle, thus terminating her amenorrhea, had she not become pregnant.

2. *Individualization.*—The knowledge that no two patients ever present the same problem in the same manner is of equal importance with the elimination of organic disease prior to instituting treatment. The importance of individual treatment is clearly emphasized by the varying treatment of the same disorder at different age levels. Moreover, treatment must not only be directed toward the disorder in question but the therapeutic regimen must be so instituted that the associated constitutional derangements are also aided. It is an all-important fact that a patient is not wholly composed of selected endocrine glands.

3. *Evaluation of the Pathologic Physiology.*—A working knowledge of the normal menstrual cycle, of the mechanisms which evoke menstrual irregularities, and of the pharmacologic properties of the numerous endocrine products now available is of paramount importance in the treatment of any menstrual irregularity. When confronted with such an abnormality, the physician must carefully evaluate the possible



endocrine imbalance involved and select the proper agent for its correction. Without an appreciation of the physiologic responses evoked by the therapeutic measures to be applied, any routine of treatment proposed for the dysfunctional amenorrhea remains perfunctory and haphazard.

4. *Early Treatment.*—Continued malfunction of one endocrine gland may, because of the close interrelationship of the glands to one another, result in disturbances in totally unrelated organs. Far-reaching systemic effects may follow in the wake of what appears to be an innocuous menstrual disorder. For instance, amenorrhea of either pituitary or ovarian origin may culminate in such marked uterine atrophy as to further prolong the amenorrhea at a time when the original endocrine disorder has already been eliminated. It is, therefore, axiomatic that treatment be applied as soon as possible. If this dictum were more widely appreciated, there would be a lessened incidence of sterility of endocrine origin.

#### DYSFUNCTIONAL AMENORRHEA

Amenorrhea, just as dysmenorrhea and as menorrhagia, is merely a symptom of either a constitutional or a local disorder. It is the unphysiologic absence of menstruation. When it is of short duration (two or three months), it is termed oligomenorrhea. Amenorrhea may be called *primary* when menstruation had never appeared, and *secondary* when menstruation had previously been present. From our knowledge of the mechanism of normal menstruation, it is apparent that amenorrhea may arise from either an organic or a functional defect in any of the interdependent organs whose harmonious activity controls the menstrual cycle, namely the anterior hypophysis, the ovary and the uterus. Moreover, disturbances of endocrine glands other than the anterior hypophysis and ovaries, as well as nonendocrine illnesses, may evoke amenorrhea indirectly by affecting the function of the three organs concerned with menstruation. Thus, hyperthyroidism may cause amenorrhea by stimulating the excretion of estrogen before it is utilized by the endometrium (Van Horn<sup>4</sup>). Likewise, starvation from any cause may evoke amenorrhea by causing pituitary deficiency.

## I. AMENORRHEA OF PITUITARY ORIGIN

Because of the pivotal position of the anterior hypophysis in the control of the menstrual cycle, it is most often the site of origin of dysfunctional amenorrhea. The pituitary cause of the amenorrhea may be either an organic one, as in adenoma, or functional, as in Fröhlich's syndrome. The latter is the leading cause of dysfunctional amenorrhea.

## The Diagnosis of Fröhlich's Syndrome

The recognition of adiposogenital dystrophy (Fröhlich's syndrome) as a cause of amenorrhea depends upon the presence of some of the cardinal features of the disorder, such as

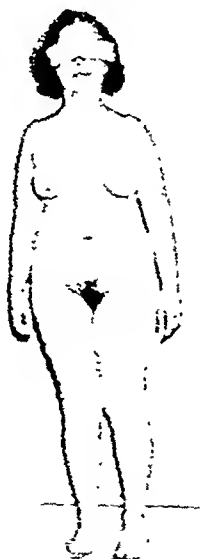


Fig. 117.—An adolescent girl who shows the early changes of Fröhlich's syndrome: mammary-mous-girdle adiposity, tapering wrists and ankles, slight facial hirsutism, and pyramidal-like pubic escutcheon.

underdeveloped genitalia, characteristic adiposity, hypertrichosis, osseous changes, a placid disposition, and headache. Occasionally, the diagnosis is aided by the finding of minor defects in the visual fields and by the use of certain laboratory tests.

*Atrophy of the generative organs* is one of the most evident consequences of hypopituitarism. The undersized genitalia vary in degree with the duration of the amenorrhea. The cervix usually presents the pinhole type of external os. The uterus is usually small, and most often acutely malflexed.

The *obesity* of Fröhlich's syndrome in the female has a distinctive distribution (Fig. 227). While it may vary in degree with each patient, it is most marked in the lower abdomen, breasts, shoulders and thighs. It is characteristic that the extremities below the knees and elbows are not adipose.

In the adult female, Fröhlich's syndrome features *hypertrichosis* of the face and limbs, in association with a pyramidal configuration (male) of the pubic hair. The hirsutism is so annoying to the average patient that it alone often brings her to the medical attendant.

The *unequal growth of the bones* found in many of the women suffering from amenorrhea of the Fröhlich's type suggests that the syndrome had its onset early in life, even though the amenorrhea had not appeared until adulthood. The patient with Fröhlich's syndrome is usually of normal height but the forearms, legs, hands, fingers and feet are relatively short. The pelvic girdle is usually heavy, of the so-called masculine type.

The *placidity* of the patient with adiposogenital dystrophy is well known. Such a patient rarely complains of anything more than the amenorrhea, hypertrichosis and obesity characteristic of the syndrome. The patient with Fröhlich's syndrome is notably free from dysmenorrhea, dyspareunia and gastro-intestinal capriciousness. The intelligence is usually average.

The "*pituitary headache*," allegedly characteristic of Fröhlich's syndrome, is not understood. It has been ascribed, without adequate proof, to organic changes in the sella turcica (Cushman<sup>5</sup>). It may be the result of some little understood metabolic change current in the disorder. It has no characteristic location.

Moderate and reversible *visual field defects* may be present for certain forms and colors in adiposogenital dystrophy.

They are not sufficiently characteristic, however, to be pathognomonic of the disorder. It is important not to confuse these minor field defects with the serious, progressive, bitemporal contractions characteristic of large hypophyseal tumors.

The *laboratory findings* which may be of use, when easily accomplished, in the diagnosis of Fröhlich's syndrome include the bio-assays for gonadotropin and estrogen, sugar and fat tolerance tests, and the determination of the specific dynamic action of protein. If one searches for gonadotropic hormone in the urine and the blood of a patient with Fröhlich's syndrome, he is not likely to find a demonstrable quantity because of the pituitary hypofunction. As a secondary manifestation, there is a diminished quantity of estrogen in both the blood and the urine of the patient. The sugar tolerance is usually high, as it is in all types of hypopituitarism. However, sugar tolerance is influenced by so many extrapituitary factors as to be unreliable as a diagnostic test (Eidelsberg<sup>6</sup>). The basal metabolic rate is usually within the lower limits of normal in Fröhlich's syndrome but the specific dynamic action of protein, as determined by comparing the basal metabolic rate before and after the ingestion of a protein meal, usually fails to reach the normal level of 15 per cent (Goldzieher<sup>7</sup>).

There is no characteristic *endometrial pattern* in the amenorrhea of Fröhlich's syndrome. The degree of development of the endometrium depends entirely on the degree of ovarian function current during the period of amenorrhea and on the ability of the endometrium to respond to whatever stimulus is present. The findings in the endometrium, therefore, may range from complete atrophy to a well-developed proliferative phase. Occasionally, a secretory endometrium is found in this type of patient, in which case it must be assumed either that the patient might have menstruated had she not been curetted or that the endometrium, even though developed, is incapable of bleeding.

### The Treatment of Amenorrhea in Fröhlich's Syndrome

There is no single routine of treatment for the amenorrhea associated with adiposogenital dystrophy. The treatment must be individualized for each patient and must follow in general those therapeutic principles applicable to all types of dysfunctional menstrual disturbances. The patient usually seeks relief from one or all of the three major symptoms, namely, amenorrhea, obesity and hypertrichosis. There is no medicinal or endocrine treatment for the latter, nor is there a single therapeutic modality which will control the obesity and, at the same time, alleviate the amenorrhea. Successful treatment usually embodies, in addition to observation of the therapeutic principles outlined above, the use of several measures in combination. It is not possible to offer a com-

plete discussion of the experimental and clinical backgrounds of the many therapeutic agents currently employed in the treatment of amenorrhea of pituitary origin. Many of the measures described in the following paragraphs may be applicable alone, as well as in combination.

1. *Constitutional Measures.*—All nonspecific, hygienic procedures which will aid the patient to attain physical and mental normalcy should be employed. This is especially important for the correction of the associated obesity. Sedentary habits should be corrected by gradually increased exercises. The diet should be accurately prescribed so that it is high in protein and organic calcium but low in fat and carbohydrate (Evans and Strang,<sup>8</sup> and Kenyon<sup>9</sup>). The patient should be advised to eat liberally of lean meat, fish, eggs and cottage cheese. There should be a daily intake of two average portions of 5 per cent vegetables and of 10 per cent fruits. One pint of buttermilk or skimmed milk daily may be used to supply the required mineral salts. It is also advisable, when the diet is low in fat, to supply one of the vitamin concentrates in order to avoid any possible subclinical deficiency. The diet should be practically sugar-free, and bread must be sharply curtailed. The patient should be cautioned not to eat between meals and before retiring. It must also be emphasized that the beverages imbibed should be free from flavoring and should not exceed six average-sized glassfuls daily.

2. *Desiccated Thyroid Substance.*—Inasmuch as the basal metabolic rate in patients with adiposogenital dystrophy is usually low, though within physiologic limits, the administration of thyroid substance is indicated merely because of its stimulative effect in general. Of itself, desiccated thyroid substance has little influence on the amenorrhea but it is of value as an adjuvant in therapy. The initial dose should be small, such as  $\frac{1}{2}$  grain twice daily, irrespective of the basal metabolic rate. The dose may be gradually increased to the point of the patient's tolerance, and the maintenance dose continued at a slightly lower level. It must be remembered in prescribing thyroid substance that the commercial varieties

of the desiccated gland contain different amounts of thyroxin. In order, therefore, to insure accurate dosage and to prevent toxic reactions, the same brand of the substance should be requested in renewal prescription.

3. *Estrogen*.—The use of estrogen alone in the treatment of the amenorrhea of Fröhlich's syndrome, even though it evokes a single episode of uterine bleeding, is not sufficient to correct the basic disorder. Estrogen, it must be remembered, does not stimulate either the ovaries or the pituitary gland. The objective of estrogen therapy in any type of amenorrhea is to combat the associated uterine hypoplasia. In Fröhlich's syndrome, the associated uterine atrophy may reach such a degree that, even if the pituitary function is restored through the use of other therapeutic agents, menstruation fails to occur because of the lack of uterine responsiveness. Herein lies the usefulness of estrogen. The dosage should be that amount which will raise and maintain the quantity of circulating estrogen to the normal premenstrual level. Small doses, no matter how administered, produce moderate growth and vascularity of the uterus but do not inhibit pituitary function.

The dosage of estrogen employed as an adjuvant to other measures in the treatment of pituitary amenorrhea varies with both the mode of administration and the type of estrogen employed. Either the natural or the synthetic estrogens may be employed. The *natural estrogens* include several, highly potent compounds designated in their order of potency as estradiol, estradiol benzoate, estradiol propionate, estrone and estriol. When administered hypodermically for the purpose under discussion, the dose of natural estrogen should be approximately 5000 international units (estrone) every fourth day. Whenever possible, estrogen should be given orally. The chief advantage of the oral route, aside from the economic factor and the ease of administration, is that it more closely imitates nature by supplying small quantities of the hormone continuously. The oral dosage of the natural estrogen should be from 1000 to 2000 international units (estrone) daily for a period of approximately three months. A clarifi-

TABLE 1  
THE NATURAL ESTROGENS

Commercial Source	Estradiol	Estradiol Benzoate	Estradiol Propionate	Estrone (Theelin)	Estriol
Units, as Discussed	Extract of hog's ovaries, or of urine of pregnant mares. Also, from estrone synthetically	Synthesized from estradiol	Synthesized from estradiol	From the urine of both pregnant women and mares	Extracted from placental tissue and from urine of pregnant women
Random Commercial Types	Milligram (1 mg. equals from 10,000 to 12,000 rat units)	Int. unit, which is 0.1 gamma (1 mg. equals 5000 rat units)	Milligram (1 mg. equals about 3000 rat units)	Int. unit, which is 0.1 gamma (1 mg. equals 1000 rat units)	Day-oral unit, or in milligrams (1 mg. equals 350 rat units)
	Dimenformon Ovocycin Proxynon-DII	Dimenformon Ben-ovocycin benzoate Proxynon-II	Dimenformon dipropionate DI-ovocycin Follicero	Amniotin Estrone Theelin Follicerin Plectrin Menformon Estrofin	Theelin Estriol Ethinin

cation of the dosage of several of the commercial varieties of the natural estrogens, as employed as an assisting agent in pituitary amenorrhea, is attempted in Table 1.

From the economic viewpoint, it is expedient to employ the recently introduced, synthetic estrogen, *stilbestrol*. This substance, chemically unrelated to the sterols which constitute the natural estrogens, is potent orally. It has been established that 1 mg. of stilbestrol is equal in estrogenic activity to 5 mg. of estrone. If the patient tolerates stilbestrol, it may be administered orally to achieve the same growth and vascularity of the uterus as obtained with the natural estrogens. It is, however, capable of evoking extreme nausea and vomiting, more especially when given in doses beyond 0.5 mg. At this dosage level, namely, 0.5 mg., stilbestrol may be safely administered daily by mouth, or every fourth day hypodermically. At this level, the incidence of gastro-intestinal disturbance is less than 3 per cent (Mazer et al.<sup>10</sup>).

It may be advisable to employ estrogen in somewhat larger doses than those stated in the preceding paragraphs, at the very initiation of therapy in pituitary amenorrhea, in order to evoke a single episode of so-called withdrawal bleeding. This has the important psychologic value of instilling the desired degree of confidence in the patient and in fixing her attention to the course of treatment outlined. Caution, however, must be exerted in order to avoid giving the impression that a "cure" has been so obtained.

4. *Low-dosage Roentgen Irradiation.*—The use of low doses of x-ray for the correction of dysfunctional alterations of the menstrual cycle is one of the most valuable remedial procedures available. Although it is a purely empiric measure, inasmuch as the means of its effectiveness are unknown, the safety and the value of properly administered roentgen therapy to the pituitary gland and the ovaries has been well established in this field by the work of Rubin,<sup>11</sup> Kaplan,<sup>12</sup> Drips,<sup>13</sup> and Mazer.<sup>14</sup> The term "stimulation treatment" is often applied to this type of roentgen therapy because it is assumed that some acceleration of cellular function, without definite cytologic change, occurs as a result of the rays. It would appear, as suggested by Duggar,<sup>15</sup> that the irradiation alters the cellular activity by causing a rearrangement of the intracellular electrons, atoms and molecules.

The harmlessness of such irradiation of the pituitary gland and ovaries is attested to by the statistical results of the sev-



eral authors mentioned in the preceding paragraph. It must be remembered, however, that, while it is almost impossible to "overtreat" the pituitary gland, care must be exerted in irradiating the ovaries. The dose should be carefully controlled and the irradiation administered only by a skilled roentgenologist. Moreover, it is of paramount importance that the patient selected for this type of treatment be chosen with care. It is useless to irradiate the ovaries in the presence of amenorrhea associated with gross pelvic changes, as in chronic inflammation. It is also imperative, because of the harmful effects of roentgen irradiation on the embryo (Goldstein and Murphy<sup>16</sup>) *to exclude positively the existence of early pregnancy* prior to the administration of x-ray treatment. If the physician cannot determine the presence or absence of pregnancy to his entire satisfaction by means of physical examination, a biologic pregnancy test should be performed before the institution of treatment.

The *technic* of the irradiation has been more or less fixed by usage. Even though the ovaries are but secondarily affected in pituitary amenorrhea and despite the fact that x-ray treatment of the pituitary alone has been employed with good results, the incidence of success is heightened by the simultaneous irradiation of the pituitary gland and the ovaries. The dosage employed at both sites is from 50 to 100 r, measured in air. The proper technic, as outlined by Edeiken,<sup>17</sup> includes three treatments at weekly intervals to both the pelvis (ovaries) and the pituitary fossa. "In the patient of average size, the technical factors are 127 kv., 5 ma., 14-inch distance, 5-mm. aluminum filter for from three to five minutes. This is equivalent to 7.5 to 12.5 per cent S.E.D. or 50 to 80 r." It is important that the coexistent uterine atrophy be treated by means of small doses of estrogen at the same time that the roentgen-rays are being employed to correct the basic cause of the amenorrhea.

If one were to depend on the use of low-dosage irradiation of the pituitary gland and ovaries as the sole therapeutic agent in the management of dysfunctional amenorrhea, the results achieved would be good in secondary amenorrhea but notably poor in primary amenorrhea. The refractoriness of the latter to all modes of therapy is well known. In secondary amenorrhea, however, more than 60 per cent of the patients treated by means of the roentgen-ray are restored to menstrual periodicity. It is noteworthy that irradiation is more likely to be successful in women whose menstrual interval is from

TABLE 2  
THE AVAILABLE GONADOTROPINS

Commercial Source	Pituitary	Chorionic	Equine	Combination (Synergist)
Extracts of ant. lobe of pituitary of cattle and of sheep	Ref. units, varying with the method of assay	Obtained from human pregnancy urine and from placental tissue	Blood serum of pregnant mares	Gonadotropin-free extract of ant. lobe of pituitary added to chorionic gonadotropin
Units, as Dispersed				
Random Commercial Types		Int. unit, or the gonadotropic activity in 6 i. u. (100 gamma) of the standard	Int. unit, or the gonadotropic activity in 6 i. u. (250 gamma) of the standard	Synergy unit, which is about equal in gonadotropic activity to 20 int. units of equine gonadotropin
	Preparations Purified Gonadotropin Maturin Ambion Gonadotropic factor	Preparations Purified Gonadotropin Ambion A.P.G. Endocrine	Gonadotropin Gonadotropin Ambion	Synergist

three to four months. The percentage of responsiveness seems to vary inversely with the length of the amenorrhea.

5. *Gonadotropin Therapy*.—At the present time, there are available for clinical application four varieties of gonad-stimulating pituitary and pituitary-like substances, as shown in Table 2. While the results, as a whole, have been disappointing, gonadotropin therapy will be employed until a more satisfying agent is found.

The usefulness of *pituitary gonadotropin* is limited by the insufficient concentration and the relatively high cost of the extracts. Moreover, there seems to be an unpredictable element in the reaction of the human ovary, as compared to that of the animal ovary, following the administration of pituitary gonadotropin. As pointed out by Greenblatt and Pund,<sup>15</sup> there are certain undesirable side-reactions which occur in the stimulated ovary. When pituitary gonadotropin is employed to combat the amenorrhea of Fröhlich's syndrome, it is advisable to administer simultaneously one of the standardized pituitary extracts which contain *all* of the known hormones of the anterior hypophysis.

The administration of *chorionic gonadotropin* seems to be of no use in any type of amenorrhea. Chorionic gonadotropin merely enhances the luteinization of the ovarian follicles but does not cause the production of corpora lutea in the human ovary.

*Equine gonadotropin*, because of its proved ability to evoke a complete ovarian cycle in the normally responsive ovary (Davis and Koff,<sup>19</sup> and Siegler and Fein<sup>20</sup>), may be employed in pituitary amenorrhea as a temporary substitutive agent. Such treatment will not, of course, correct the basic pituitary hypofunction responsible for the disorder but may evoke isolated episodes of uterine bleeding. The dose of equine gonadotropin in the treatment of amenorrhea of pituitary origin is 500 international units, given intramuscularly every other day for 10 injections. Such a course of treatment may be repeated several times, provided a rest period of at least three weeks is permitted between courses. There is a notable lack of enthusiasm for the use of this substance in the treatment of amenorrhea (Gray,<sup>21</sup> and Greenblatt and Pund<sup>16</sup>).

The recently introduced *combined gonadotropin* (Table 2) seems to be a more promising therapeutic agent than the gonadotropins previously employed. The combination of chorionic gonadotropin with the so called "pituitary synergist" of Evans<sup>22</sup> created a substance with remarkable gonadotropic qualities. The synergistic factor, found in concentrated growth-promoting extracts of the anterior hypophysis, is of itself devoid of gonadotropic activity. When, however, it is combined with chorionic gonadotropin it seems to enhance the effectiveness of the latter one hundred-fold (Mazer and Ravetz<sup>23</sup>).

The degree of responsiveness obtained with the combined gonadotropin naturally depends upon the ability of the ovary to respond and upon the dosage of the substance employed. There is no doubt that the use of a combined gonadotropin, such as *synapoidin*, will evoke uterine bleeding in even severely amenorrheic women. Such a response may be obtained in more than 80 per cent of the patients treated with a single course of *synapoidin*, namely, 30 synergy units (2 cc.) every other day for ten injections. However, unless the basic pituitary deficiency is corrected by *other measures*, the menstrual cycle will not be resumed. The use of *synapoidin* simply evokes an ovarian response which is reflected in sufficient endometrial change as to result in uterine bleeding.

## II. AMENORRHEA OF OVARIAN ORIGIN

The amenorrhea described in the preceding paragraphs, attributable to decreased function of the anterior hypophysis, occurs because an insufficient pituitary stimulus fails to rouse the ovaries to function. The ovarian failure thus resulting is secondary to the pituitary hypofunction. There is, however, another type of amenorrhea which results from an inability of the ovaries to respond to a normal degree of pituitary function. It is apparent that, even though there is sufficient pituitary gonadotropin circulating in the blood, the production of the ovarian hormones, estrogen and progesterin, is essential to the normal progress of events which results in the menstrual cycle. The ovarian derangement which causes a lack of ovarian responsiveness to pituitary gonadotropin is usually dysfunctional in origin, rather than organic. Such an inherent or an acquired inability of the ovaries to produce follicles and corpora lutea represents a "primary ovarian

failure," in contradistinction to the secondary failure resulting from the lack of pituitary function.

Primary ovarian failure may result either from a congenital inability of the ovaries to grow or from a disorder acquired during early womanhood which caused sufficient change in the ovarian structure to prohibit normal function. Primary ovarian failure, when encountered in the adult female, may be either of the two types mentioned.

#### The Diagnosis of Primary Ovarian Amenorrhea

The *congenital* variety of ovarian amenorrhea is accompanied by certain physical changes because of the time of onset of the disorder. Inasmuch as the ovaries are congenitally deficient, the pubertal changes in skeletal growth are disorganized. Estrogen is an important factor in controlling the skeletal changes at puberty because of its effect on epiphyseal union. The presence of estrogen tends to cause closure of the epiphysis, thus limiting the growth of the long bones. The absence of estrogen, a condition characteristic of congenital ovarian failure, permits the epiphysis to remain open and, therefore, to respond to the normal quantity of hypophyseal growth hormone. This causes the long bones to grow to abnormal lengths. This change does not affect the bones, such as the ribs, vertebrae and sternum, which do not grow from epiphyses. For this reason, the congenital hypogonad has long limbs. Moreover, because of the lack of overgrowth of the short and flat bones, the development of the chest appears disproportionately small, resulting in a lanky, flat-chested individual. At the same time, the lack of estrogen results in poorly developed secondary sex characteristics and underdevelopment of the genital organs. The resultant combination gives to the congenital hypogonad the characteristic eunuchoid habitus which is recognizable by the unusual length of the extremities, undeveloped breasts, and a lack of pubic hair (Fig. 228).

The *acquired* variety of primary ovarian failure is not associated with any of the somatic changes which characterize the patient with the congenital type of disorder. Inasmuch as the condition develops after growth has ceased, during

adolescence and early adulthood when infections, improper diet and constitutional diseases affect the female, there is no associated alteration in stature. There is, however, a similar degree of genital hypoplasia. Such undergrowth of the generative organs is not diagnostic because it occurs in all types of ovarian failure, whether primary or secondary.

It is interesting to note that the patient with amenorrhea resulting from primary ovarian failure presents entirely dif-

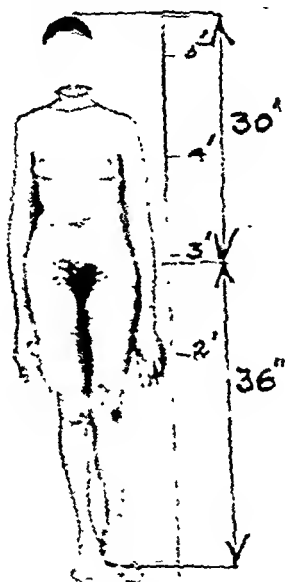


Fig. 228.—An amenorrheic Negress, aged twenty-four years, who shows the typical configuration of primary hypogonadism. Note the lean figure, flat chest, small breasts, scanty pubic hair, and the tremendous length of the long bones.

ferent mental and physical characteristics from those exhibited by the woman with secondary ovarian failure of pituitary origin. The latter, as noted in the earlier paragraphs, exhibits a characteristic type of obesity, hypertrichosis, and an especially well-balanced nervous system. The primary hypogonad, on the other hand, is characteristically underweight, hyperemotional, overcritical, possessed of a high-pitched

failure," in contradistinction to the secondary failure resulting from the lack of pituitary function.

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to the treatment of Fröhlich's syndrome, serves to increase the responsiveness of the uterus to a degree that permits it to continue to function when the endocrine disorder has been corrected. Inasmuch as the purpose of the estrogen is the same as when it is administered in pituitary amenorrhea, the dosage and means of administration are the same as described for that disorder.

3. *Low-dosage Roentgen Irradiation.*—The dysfunction of the ovaries which gives rise to primary ovarian failure and amenorrhea responds well to the low-dosage type of x-ray therapy. The technic and quantity of irradiation are the same as described in the treatment of Fröhlich's amenorrhea. There is, however, no need to irradiate the pituitary gland when the disorder arises only in the ovaries. When there is not a clear-cut distinction as to which of the glands, pituitary or ovary, is primarily responsible for the amenorrhea, it is best to irradiate both sites. Irradiation of the pituitary gland can do no damage, especially in the roentgen values employed.

4. *Insulin.*—The administration of insulin has been advocated in the treatment of dysfunctional menstrual disorders for many years (Klaften,<sup>24</sup> Vogt,<sup>25</sup> Liegner<sup>26</sup> and others). The hypodermic administration of insulin in doses varying from 8 to 15 units daily for several months seems to be most effective in the amenorrhea associated with malnutrition and asthenia. It is an unsettled question as to whether the insulin acts directly by stimulating the ovaries (Mazer and Katz<sup>27</sup>), or indirectly by increasing appetite, weight and well-being (Blotner<sup>28</sup>). The restoration of normal menstruation and the improved state of nutrition seem to occur concomitantly. The use of insulin in amenorrhea should be restricted to the thin, undernourished woman, and the dosage individualized according to the patient's tolerance. Proper dietary instructions, namely, an increased intake of carbohydrates, must be given to the patient. One of the major difficulties in the employment of the insulin treatment is the objectionable necessity of daily hypodermic injections for a period of several months. Even if the patient is able to master the technic of self-injection, she frequently objects to the daily hypodermic.

5. *Surgery.*—There are three surgical measures which are



voice, and afflicted with a markedly unstable autonomic nervous system which makes her the frequent victim of dysmenorrhea, dyspareunia and dyspepsia. More often than not, the latter triad of symptoms is the patient's chief complaint.

None of the routine diagnostic *laboratory procedures* are of value in differentiating the amenorrhea of primary and of secondary ovarian failure. Bio-assay of the quantities of estrogen present in the blood and the urine are of no diagnostic value, inasmuch as the values are low in ovarian failure of *any* origin. The demonstration, however, of an excess quantity of pituitary gonadotropin in the patient's blood suggests that the amenorrhea may be of ovarian origin. If it were amenorrhea resulting from pituitary deficiency, such an excess would not be present. Moreover, it is an accepted fact that the lack of estrogen production by the ovaries results in an increased production of pituitary gonadotropin. In the average type of office practice, it is not feasible to perform such laboratory assays. The physician must, therefore, depend upon the differential diagnosis afforded by the patient's past history, body contour and psychic state.

### The Treatment of Amenorrhea of Ovarian Origin

Several of the agents employed in the treatment of amenorrhea of Fröhlich's syndrome are also useful, paradoxical as it may seem, in the management of the amenorrhea caused by primary ovarian failure. There are, in addition, a few therapeutic measures which are useful in the ovarian type of amenorrhea alone. The modalities employed are summarized in the following paragraphs.

1. *General Measures.*—The importance of a well-balanced diet, one containing an adequate number of calories and a sufficient quantity of vitamins, cannot be overemphasized. This simple measure is especially valuable in the management of the young hypogonad who is usually the victim of her adolescent circumstances, suffering from an overburdensome amount of school work and extramural duties. The hyperemotional state of these patients is such as to influence the proper selection of foods. It is imperative that the patient be made to understand the value of meat, milk, butter, cream, green vegetables and eggs.

2. *Estrogen.*—The value of estrogen in the regimen intended for the amenorrhea of ovarian origin lies in its recognized ability to combat the associated uterine atrophy. The administration of estrogen, as outlined in the section devoted

to the treatment of Fröhlich's syndrome, serves to increase the responsiveness of the uterus to a degree that permits it to continue to function when the endocrine disorder has been corrected. Inasmuch as the purpose of the estrogen is the same as when it is administered in pituitary amenorrhea, the dosage and means of administration are the same as described for that disorder.

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## III. AMENORRHEA OF UTERINE ORIGIN

Normal menstruation is, as mentioned previously, entirely dependent upon the responsiveness of the endometrium to the ovarian hormones, the secretion of which is governed by the function of the anterior hypophysis. The amenorrhea arising in dysfunction of the pituitary gland and ovaries has already been described. It must also be apparent that the uterus, an equal link in the menstrual chain, may be the only seat of disorder. If the endometrium fails to respond to hormonal stimulation, the menstrual cycle is interrupted.

## The Diagnosis of Amenorrhea of Uterine Origin

The lack of responsiveness of the endometrium may be either congenital or acquired. When the uterus is *congenitally* underdeveloped, the patient never menstruates (primary amenorrhea). In such patients, the uterus may *totally* lack the ability to grow and to bleed. Consequently, primary amenorrhea is most refractory to treatment.

The *acquired* variety of endometrial nonresponsiveness may have its origin in an antecedent amenorrhea of long standing which gave rise to such a degree of atrophy that, even when the normal endocrine state is attained, bleeding fails to occur. The endometrium may also acquire a severe degree of nonresponsiveness following an acute endometritis resulting from postabortal or puerperal infection. It should also be recalled that the intra-uterine application of radium, even though the dose is small, may occasionally cause permanent sclerosis of the endometrial arteries. Thus, it is possible that the endometrium in radium-sensitive patients may be completely devascularized by as little as 250 milligram-hours.

Zondek<sup>24</sup> described the amenorrhea of uterine origin as "polyhormonal amenorrhea" because it is characterized by endometrial nonresponsiveness in the presence of adequate quantities of circulating estrogen. Therefore, the diagnosis of uterine nonresponsiveness as the primary basis for amenorrhea depends on the finding of both endometrial atrophy in a specimen obtained by curettage and at least 1 mouse unit of estrogen in 40 cc. of the patient's blood, or of 15 rat units of active estrogen in at least one of four weekly urine assays (Fig. 229).

employed with varying frequency in the treatment of ovarian amenorrhea—uterine curettage, dilatation of the cervix, and resection of the ovaries.

The diagnostic value of *uterine curettage* is unquestioned in menstrual disorders but its use as a therapeutic measure is not often justifiable in amenorrhea. Curettage alone will often cure certain types of menstrual disorder characterized by excessive uterine bleeding. It will do little in the treatment of amenorrhea.

The value of *mechanical dilatation of the cervix* in the treatment of gonadal deficiency was stressed a decade ago by Halban<sup>29</sup> and Cary.<sup>30</sup> It is possible that increased ovarian activity follows prolonged cervical dilatation in the human, as in the animal (Long and Evans<sup>31</sup>), and that such stimulation may be of therapeutic value. Mechanical measures, such as cauterization of a grossly infected cervix, may have some value in improving the circulation of the ovary. Chronic cervical infection may cause thickening of the ovarian surface by reason of chronic ascending infection, and such thickening may impede the normal progress of follicular growth. Certainly, if a cervical infection is present, it should be treated.

*Resection of the ovaries*, more especially if those organs are palpably polycystic, has been advocated (Robinson,<sup>32</sup> and Stein and Leventhal<sup>33</sup>). The technic is simply to excise wedge-shaped portions of each ovary, thereby removing the multiple follicle or luteal cysts and thus relieving intra-ovarian pressure. Any such treatment, requiring a laparotomy, is not a simple remedy applicable to many women and should, therefore, be relegated to that small group of women whose menstrual disorder fails to respond to the single or combined use of other remedial agents.

6. *Gonadotropins*.—The administration of pituitary, pituitary-like and equine gonadotropic substances has no place in the treatment of amenorrhea resulting from primary under-function of the ovary. Such therapy would be illogical because there already exists an excess of pituitary gonadotropins in the patient's blood stream. The administration of additional gonadotropin would not help in correcting the ovarian defect.

logical degree of uterine atrophy giving rise to uterine amenorrhea, it is necessary to administer large doses such as 10,000 rat units (or 100,000 international units of estrone) every third day for five doses. If bleeding is induced, one should not give further medication in the hope that the uterine mucosa has been sufficiently stimulated to respond to the level of ovarian hormones circulating in the patient's blood. If bleeding is not induced by such acutely administered large doses of estrogen, the course of injections should be repeated at least twice. It should be recalled that this therapy is not uniformly effective, failing especially in the congenital variety of uterine atrophy, or primary amenorrhea.

#### SUMMARY

A brief review of the endocrine causes of amenorrhea is presented. It is emphasized that normal menstrual function is dependent upon the harmonious activity of the pituitary gland, ovaries and uterus, as well as the close relationship between these organs and the nervous system.

The amenorrhea of pituitary hypofunction, commonly termed Fröhlich's syndrome, is described. Its diagnosis is shown to depend upon the recognition of certain physical characteristics and laboratory findings. The treatment is outlined to include the use of constitutional measures, desiccated thyroid substance, estrogen, low-dosage roentgen irradiation, and gonadotropins.

It is stated that the ovaries per se may give rise to amenorrhea by failing to respond to the pituitary stimulus present. Such primary hypogonadism is shown to be associated with certain physical characteristics and to respond frequently to many of the measures employed in the treatment of pituitary amenorrhea. A notable exception to the latter statement is the use of gonadotropic substances, which is contraindicated in amenorrhea of ovarian origin.

Amenorrhea of uterine origin is included in this presentation even though it is not, strictly speaking, an endocrine disorder. Such amenorrhea, ascribed to either a congenital or an acquired lack of endometrial responsiveness, is described as occasionally responding to huge doses of estrogen.

### The Treatment of Uterine Amenorrhea

There is no reason in amenorrhea caused solely by uterine deficiency for the administration of endocrine substances other than estrogen. The patient with amenorrhea of uterine origin already possesses a degree of ovarian function as evidenced by repeated blood and urine hormone titrations, and lacks only a responsive endometrium. Treatment, then, should



Fig. 229.—Photomicrograph of the nonresponsive, atrophic endometrium of a woman, aged twenty-five years, who had never menstruated. At the time of this biopsy, the patient excreted more than 20 rat units of estrogen in the twenty-four-hour output of urine. Subsequent treatment with as much as 3,000,000 international units of estrone failed to evoke a single episode of uterine bleeding. ( $\times 100$ .)

be directed toward the stimulation of the uterus because, if the uterine atrophy is overcome, the menstrual cycle may be reestablished. It is not enough under these circumstances to administer the estrogen as it is employed in the treatment of ovarian and pituitary amenorrhea, in which disorders only maintenance doses are required. In the presence of the patho-

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## DIAGNOSIS AND TREATMENT OF STERILITY IN THE MALE

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In propagation of the species the male has two requirements to fulfill. He must produce sperm cells of good quality in sufficient number and must ejaculate them properly. The first requirement is indispensable since a male who does not possess functioning spermatozoa is incapable of impregnating. The second is a relative requirement. The semen should be ejaculated against the cervical os, but inability to project it here is not an absolute hindrance to pregnancy since sperm cells ejected anteriorly may be able to progress to the cervix. Insemination is not possible when spermatozoa are prevented by obstructions from entering the seminal fluid.

### THE CAUSES OF MALE STERILITY

The causes of male sterility may be divided into two groups: (1) conditions which prevent or impede sperm ejaculation; (2) conditions which adversely affect the sperm cells.

#### Impediments to Sperm Ejaculation

*Impotence.*—The most frequently encountered impediment to ejaculation is impotence. This may be partial or complete. It may be due to organic lesions of either the genital apparatus or the nervous system. In this event the possibility for alleviation depends upon whether or not the primary cause can be corrected.

The ordinary type of impotence does not depend upon a recognizable organic lesion. In some cases it is entirely emotional in character. For example, a man has extramarital intercourse and then becomes fearful of having contracted a

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venereal disease. He becomes impotent. When he is convinced that he is not diseased he promptly regains his potency.

The usual history in cases of impotence is that of more or less gradual decline of desire and vigor. The first noteworthy changes may consist of premature ejaculations or of difficulty in obtaining erections. It is quite likely that the fault is often in the higher brain centers. Apparently the power to respond to sexual stimulation has been lost, perhaps irrevocably. This type of impotence may therefore be considered *psychic* in nature. It may be part of the symptom complex in psychoneurosis. Sometimes the onset of impotence will precipitate other psychoneurotic manifestations.

Treatment of this form of impotence is generally unsatisfactory. Recitals of cures brought about—after everything else had failed, of course—by giving the patient an injection which he is impressively told was secured by great effort and was a positive restorative, always remind me of the late Dr. J. C. DaCosta's story of the inmate at the Philadelphia General Hospital whose only complaint was that he had a litter of kittens in his stomach. A house officer with an investigative turn of mind administered an emetic and surreptitiously poured the vomitus over a litter of kittens which he then exhibited to the patient as proof of cure. The patient felt better until the next day when he said that somehow or other several alarm clocks had gotten into his stomach.

From the foregoing it is not to be inferred that treatment is not indicated in cases of this group. But it should be recognized that often the sole service that can be rendered is to try to help the patient adjust himself to an unalterable state. This is usually accomplished only after the patient has convinced himself that everything reasonable has been done.

Measures designed to improve the patient's physical condition and to induce mental tranquility are indicated. The patient should be advised to seek sexual rest; to abstain from attempts at intercourse and to refrain from indulgence in sexual stimulation through either internal or external excitants. If there is congestion or infection in the adnexal organs it should be corrected. Treatment with male sex hormone preparations has very occasionally been of limited help.

The good effect has been in enhancement of the patient's feeling of well-being rather than in improvement of his sexual disability.

**ILLUSTRATIVE CASE.**—R. M., a white male thirty-nine years of age, complained of poor libido. This lack of desire for sexual relations worried him. He felt nervous and irritable and tired easily. He felt ambitionless and depressed. Physical examination was essentially negative except that the testes were small. However, secondary sex characteristics were fairly normal. A 75-mg. pellet of testosterone\* was implanted subcutaneously. Shortly thereafter he had a brief period of sexual activity. He also felt much better generally. He slept better, felt more settled mentally and was able to work more steadily. The feeling of fatigue decreased noticeably.

At the end of four months, a pellet of 150 mg. of testosterone was implanted subcutaneously. This had no additional effect on his sexual powers or his sense of well-being. The good effects of the first implant continued.

*Congestion of the Prostate or Seminal Vesicles.*—Congestion of the prostate and sometimes also of the seminal vesicles, which may or may not be associated with infection, is frequently present in cases of impotence and must be considered a contributing cause. Since the prostate and vesicles are part of the male sexual apparatus it is understandable that disorders of these organs may lead to derangement of the sexual act. This adnexal congestion is particularly apt to be present in cases of premature ejaculations or incomplete erections. Endoscopic examination usually reveals congestion of the prostatic urethra with edema of the verumontanum. Massage of the prostate and vesicles at weekly or semiweekly intervals, depending upon the degree of prostatic "bogginess" found on rectal palpation, is sometimes followed by increased potency. This treatment should be supplemented by advice designed to aid the general health and sexual hygiene as previously mentioned.

*Obstruction to the Passage of Semen.*—Obstruction to the passage of semen or deflection from its natural course because of local abnormalities may cause sterility. Injury to the ejaculatory ducts incidental to prostatic operations may result in passage of the ejaculate backward into the bladder. Urethral strictures of small caliber may impede the flow of semen to a degree sufficient to prevent its reaching the cervix.

\* Pellets of testosterone were supplied by Dr. Max Gilbert of the Schering Corporation, Bloomfield, N. J.

**ILLUSTRATIVE CASE.**—J. S., a white male thirty-two years of age, had a urethro-anal sinus which he said had been present since shortly after birth and resulted from an incision which was made to relieve anal obstruction. Voiding had always occurred mostly through the sinus. After his marriage it was found that the semen also was ejected through the abnormal opening. Urologic studies revealed bilateral hydronephrosis and hydro-ureter with resultant impaired renal function, a calculus in the prostatic urethra and a filiform stricture of the bulbous urethra. The urine contained albumen +4, red blood cells and myriads of leukocytes. Urine culture revealed a growth of *Bacillus coli*.

Treatment consisted of a suprapubic cystostomy, removal of the stone from the prostatic urethra and prolonged suprapubic drainage to improve the renal function. Internal and external urethrotomy was then performed. This resulted in normal semen passage, and shortly after the patient was discharged from the hospital his wife became pregnant.

*Obstruction to the Passage of Sperm Cells.*—The seminal fluid may be devoid of spermatozoa for the reason that these cells are prevented from leaving the epididymis because of the presence of bilateral stricture of the vas deferens. This condition is usually due to an antecedent bilateral gonococcal epididymitis. Sangree<sup>1</sup> cites a case of this sort in which the causative factor was an industrial accident. The continuity of the seminal passages may sometimes be reestablished by an epididymovasostomy.

It is of diagnostic importance to differentiate this condition from absence of sperm cells in the semen due to deficient spermatogenic function.

#### Disturbances of Spermatogenesis

*Normal Semen.*—Fresh seminal fluid is an opaque viscous fluid which liquefies on standing. An ejaculation normally consists of from 2.5 to 5 cc. Each cubic centimeter should contain from 20,000,000 to over 200,000,000 spermatozoa. About 75 per cent of these should be actively motile and normal in morphology. Activity should be maintained by most of the cells for at least eight hours at room temperature.

Meaker<sup>2</sup> states that normally the sperm content of semen is not constant and that the causes of variations are not known.

At least two examinations of the semen should be made whenever the husband is suspected of responsibility in a childless marriage.

*Abnormal Spermatogenesis.*—Derangements of the sperma-

togenic function will be evidenced by abnormal changes in the sperm content of the semen. There may be complete absence of sperm cells in the semen; this is called *azo-spermia*. The spermatozoa may all be dead; this is called *necrospermia*. The number of spermatozoa may be greatly reduced; this is called *oligospermia*. There may be an increase in the number of abnormally formed sperm cells.

*Maintenance of the Spermatogenic Epithelium.*—It is now generally accepted that the anterior pituitary gland secretes a hormone which is necessary to activation of the endocrine-producing cells of the testis. This activating principle is called a *gonadotropic hormone*. Whether it also directly stimulates the seminiferous tubules or whether they are supported by the testicular endocrine is not known. However, in cases of anterior pituitary hormonal deficiency there are resultant atrophic changes in both the interstitial cells and the tubular epithelium of the testes. It may therefore be concluded that the gonadotropic hormone of the anterior pituitary has either a direct or an indirect supportive influence on the spermatogenic epithelium.

The *thyroid gland* also appears to have a relation to spermatogenesis, but it is not clear whether this is direct or whether it involves the metabolic function of the thyroid. A basal metabolic determination is advisable in cases of suspected lowered fertility.

Spermatogenesis does not completely develop in patients with *cryptorchid testes* but may be expected to become established if the cryptorchidism is corrected before puberty. This fact makes it appear likely that if the tubular epithelium of the testis is kept from full development by a pathological condition existing at the time of puberty, the damage done will be irreparable.

#### DIAGNOSTIC METHODS

##### Examination of the Semen

Weisman<sup>3</sup> has well said that "the most important and the most common test performed on the male partner in an involuntarily barren marriage is the semen examination." The specimen should be collected in a clean, dry, glass container.



This can usually be done by withdrawal just before ejaculation. When this is impossible a condom may be used but the specimen should be transferred to a glass receptacle immediately after ejaculation. Otherwise the powder dusted in rubber condoms is apt to kill the sperm cells. Instruction is also given the patient that he is not to subject the specimen to heat. He is told to bring the specimen in for examination within one or two hours after it is collected.

The amount of the semen and its degree of viscosity are noted. A scant watery discharge is almost invariably deficient in sperm cells. A specimen which is so thick as to be almost gelatinous and which liquefies only slightly may be the cause of sterility because the spermatozoa are entangled. A drop of semen is examined microscopically to determine the approximate degree of multiplicity and activity of the sperm cells and whether abnormal forms appear to be in excess. A drop is examined at intervals during a period of eight hours or longer to see if activity is maintained.

By using a suitable diluent and the apparatus for making leukocyte counts, the number of sperm cells in a cubic centimeter of semen may be calculated. Special stains are used on prepared slides of the semen to study the morphology of the spermatozoa.

In semen specimens which are devoid of sperm cells, the question arises whether they are not formed at all or are formed but kept from the ejaculate by strictures of the vasa. The physical findings may furnish the answer.

If the testes are atrophic and there is a history of bilateral mumps orchitis, or if there are concomitant signs of hypogonadism, then it is almost certain that spermatogenesis is deficient. If there is a history of a bilateral gonococcal epididymitis it is likely that resultant obstruction in the vasa is the cause of the azo-ospermia.

#### Procedures in Doubtful Cases

There are three procedures which may be used in doubtful cases of male sterility to determine whether the testicular epithelium is elaborating spermatozoa. Through an opening in the scrotum the epididymis may be incised to secure a few

drops of fluid for immediate microscopical examination. A sterile needle of large caliber may be plunged into the testicle. By attaching a syringe and pulling back on the plunger as the needle is withdrawn, a little secretion from the tubules may be obtained for examination. The third method is that employed by Charney<sup>5</sup> to obtain a small piece of testis tissue for biopsy.

In those instances in which examination of properly collected seminal fluid shows all or almost all of the sperm to be inactive, it is advisable to perform a *Huhner test*<sup>6</sup> before making a diagnosis of necrostermia. Huhner's method is to examine the cervical mucus for viable spermatozoa at varying intervals after coitus. If active sperm are found here several hours after intercourse when the semen specimens show necrostermia, it is obvious that the latter finding must be due to an extrinsic factor.

## TREATMENT

### General Measures

Meaker<sup>2</sup> has emphasized the desirability of improving the general health in men who are apparently infertile. He advocates correction of slight degrees of anemia if this is present and attention to foci of infection. Chronic infections of the prostate and seminal vesicles should be properly treated.

If the basal metabolic rate is subnormal, desiccated thyroid should be administered. The starting dosage may be  $\frac{1}{2}$  grain by mouth three times a day, to be increased to a dosage sufficient to raise the metabolic rate to within the normal range.

### Gonadotropins

In 1933 Brosius and Schaffer<sup>7</sup> reported that by means of intramuscular injections of the gonadotropic principle of pregnancy urine, active spermatozoa were caused to appear in the semen of a man whose semen previously had contained none. This patient was thirty-three years of age and had testicular atrophy from mumps orchitis at the age of twenty-seven years. Other reports appeared subsequently in which excellent effects were obtained with gonadotropic hormones

in patients in whom the seminal fluid was markedly abnormal. However, comparable results were not secured by others. Weisman<sup>3</sup> says, "Altogether, this type of therapy in my cases has proved disappointing, with little improvement."

It seems to me that there is one phase of this therapeutics which has not received the attention it should. Gonadotropins are activators. In order to be effective something must be present which is capable of being activated. In other words, if conditions are such that a response is not elicitable, then the activating principle cannot be expected to be effective.

The patient of Brosius and Schaffer<sup>7</sup> was twenty-seven years of age when his testicles were affected. Presumably, spermatogenic development had been normal prior to this attack. This is altogether different from spermatogenic epithelial damage due to a condition antedating puberty since, as already stated, if the testicular tubules are prevented from developing normally during adolescence they cannot subsequently be restored to functional activity. It is obvious that gonadotropic therapy is contraindicated in conditions of this sort because there is no hope of success. It is also a fact that normal spermatogenic epithelium may be irreparably damaged by conditions arising after puberty. For example, bilateral inguinal herniorrhaphy may bring about testicular vascular changes sufficient to depress the spermatogenic function beyond repair. However, I am convinced that there are cases similar to that of Brosius and Schaffer in which gonadotropins are effective in stimulating spermatogenesis. There are two reasons why I do not generally advocate this form of treatment. It is impossible to tell in advance whether or not the injections will be beneficial and it is not certain that the stimulation is ever complete. That is to say, the spermatozoa produced by this method do not appear to be capable of impregnating.

My present practice is to advocate a trial of gonadotropins in cases in which the patients want everything possible done. There are *three types* of gonadotropins available from commercial sources at present: (1) gonadotropic material extracted from animal pituitary glands, (2) gonadotropic material prepared from the blood serum of pregnant mares. (3)

gonadotropic material extracted from human placentas and from the urine of pregnant women. My experience has been confined almost wholly to the last named, and subsequent statements apply to this type of gonadotropin. I use 200 rat units injected intramuscularly twice weekly and tell the patients that at least twelve weeks of treatment are required before a result can be expected. In cases of azo-spermia I do not recommend continuance beyond fifteen weeks if sperm have not been produced. The same advice is given in cases of necrospermia if activity is not brought about within the period mentioned. In cases in which there is an improvement in the number or activity of the sperm cells in the semen, the injections are continued until the maximum effect has been maintained for sufficient time to permit of a good test of the possibility of insemination.

Occasionally the effect produced is deleterious. I have previously reported a case of oligospermia in which injections of placental gonadotropin caused total disappearance of sperm cells from the semen.

#### SUMMARY

*History.*—Ask about conditions which may have affected the testicles: delayed puberty, injuries, mumps orchitis; and venereal disease, especially bilateral epididymitis. Also ask whether there is difficulty in intromission because of faulty erections.

*Physical Examination.*—Look for signs of hypogonadism, conditions which might impede or misdirect the ejaculate, atrophic testicles, indurated epididymis (may be tuberculous or due to previous epididymitis), urethritis, prostatitis, seminal vesiculitis or urethral stricture. Also look for correctable conditions which might influence the general health.

Determine the basal metabolic rate. If low, raise to normal with thyroid extract therapy.

If the first semen examination shows abnormalities, examine at least one more specimen. If no spermatozoa are present, determine whether this is due to deficient spermatogenesis or to strictured vasa. If spermatozoa are dead, perform Huhner test to make sure that actual necrospermia exists.

*Treatment.*—Improve the general health; improve sexual function. Administer thyroid medication if indicated. Eradicate genital infections. Correct abnormalities which may interfere with sperm ejaculation. Consider epididymovasostomy if bilateral stricture of the vas deferens is present. Gonadotropic therapy should be tried if spermatogenic function is deranged.

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## DIAGNOSIS AND TREATMENT OF TESTICULAR DEFICIENCY—MALE HORMONE THERAPY\*

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### ETIOLOGY OF MALE HYPOGONADISM

MALE hypogonadism is an endocrine disorder due to a deficient secretion by the testis of its hormone, testosterone. Because the glands of internal secretion are an interrelated system, a disorder or deficiency in one member of this system may, and frequently does, result in a complex endocrine state, even though the first clinical impression is that a simple endocrine disorder exists.

By its name male hypogonadism indicates a simple endocrine disorder, but clinical and biological study of the disorder reveals that it is more frequently a complex endocrine disorder. In the greater number of instances, it must, from an endocrinological standpoint, be considered a *secondary hypogonadism*; and in a lesser number of cases a *primary hypogonadism*.

The distinction between primary and secondary hypogonadism is based upon proved principles of endocrine physiology. It has been definitely established that the anterior pituitary lobe produces and secretes into the blood stream the gonadotropic factor. This gonadotropic factor, believed to be produced by the basophile cells, is the hormonal force which develops and maintains the hormone production of the sex glands in both sexes. The gonadotropic factor is separable, biologically, into two fractions, known as prolan A (follicle-stimulating hormone), and prolan B (lutinizing hormone). In the male, prolan A is considered to be the activator of the

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interstitial cells. Prolan A and B are both concerned in spermatogenesis. Recent findings indicate that both factors are required for activation of sex gland physiology and function, there being a synergistic action operating between the two fractions present in the gonadotropic factor.

In the majority of cases of young male hypogonads the endocrine deficiency, although manifestly a primary hyposexual state, is found on analysis to be basically a primary anterior pituitary deficiency. The hypogonadism resulting from a deficient secretion of the anterior pituitary gonadotropins can be demonstrated by urinary bio-assay. Accordingly, this form of hypogonadism is a secondary type.

Primary hypogonadism on the other hand is caused by a developmental defect existing in the testes, by destructive changes resulting from a disease of the testes themselves or as a result of an injury to its structures, or by pathological changes induced in the testes by a virus or an infection in the blood stream secondary to some primary systemic disease.

An induced state of total primary hypogonadism results from bilateral castration. In primary hypogonadism, the urinary bio-assay for gonadotropins demonstrates the presence of amounts of gonadotropic factor sufficient to maintain normal testicular function. The defect is, therefore, in the testes; that is, the testicular tissue may be unresponsive to gonadotropic stimulation, or there may be insufficient functioning tissue. This internal secretory capacity, or testosterone output, of the testes is determined biologically or by urinary assay for androgen and/or 17-ketosteroids; or clinically, by the biophysiological effect of testosterone in the human.

Testosterone stimulates development of the penis, scrotum, prostate and the secondary sex characteristics. It deepens the voice to normal tone, causes the appearance or normalization of absent or deficient pubic, axillary, body, extremity and facial hair, and effects changes in body metabolism by producing a positive nitrogen and electrolyte balance which results in weight gain and stimulation of muscle tissue development. Further, testosterone therapy stimulates growth in cases

of retarded growth and infantilism, though it does not retard growth or produce epiphyseal closure in cases of eunuchoidism. In all early observations the underdeveloped testes were not increased in size by testosterone therapy.

The importance of determining precisely the cause of the hypogonadism in order to establish a proper and adequate therapeutic management of male hypogonadism is apparent. It is evident that, in a hypogonadal patient in whom the basic endocrine deficiency is in the anterior pituitary, the administration of male hormone represents only a part of the endocrine therapy required because the basic defect in the gonadotropic function of the anterior pituitary remains uncorrected, and if this etiological cause is untreated it will persist into adult life. *Eunuchoidism* demonstrates how this form of anterior pituitary gonadotropic-hypogonadal deficiency may continue over a period of years and result in the classical clinical picture.

Metabolically we have the lean or the obese eunuchoid. Some eunuchoids attain greater height over the normal than others, but all have a disproportionately large extremity growth. Thus the total growth in the hypogonadal male must be analyzed, since the total height cannot be accepted as an indicator of normalcy of the growth process. Equally, the developmental deficiency and the lack of energy of muscle tissue of eunuchoidism result from the associated protein and blood chemical imbalance which occurs in testosterone deficiency. The outstanding physical feature of the eunuchoid, aside from the tall stature and sexual hypoplasia, is the lack or absence of secondary sexual characteristics (Fig. 250).

We have, therefore, in the eunuchoid the representative physical features of disturbed endocrine physiology essentially represented by male hormone deficiency. These signs of male hormone deficiency can be used in diagnosing most of the secondary hypogonadal cases occurring from childhood onwards. In spite of his marked male hormone deficiency the eunuchoid never complains of the climacteric group of symptoms. In our opinion this is an important point, since it indicates that the climacteric syndrome is more likely a disturbance in endocrine interrelationship than a mere hypotestosteronemia. In the climacteric there is a regression of the stimulatory effect of male hormone on the tissues, whereas in the chronic developmental hypogonadal case tissue regression has not occurred, nor has there been a withdrawal effect of the male sex hormone on the previously existing normal endocrine interrelationship. It is the disturbance of the endocrine interrelationship which is an important factor in the disturbed physiology and the symptoms of the climacteric.

In the clinical study of all hypogonadal cases resulting from a disturbance of the anterior pituitary-gonadal interre-



lationship, the other anterior pituitary functions must be appraised, particularly those relating to growth, development of general body structure and special and individual structures under its influence, and those relating to development

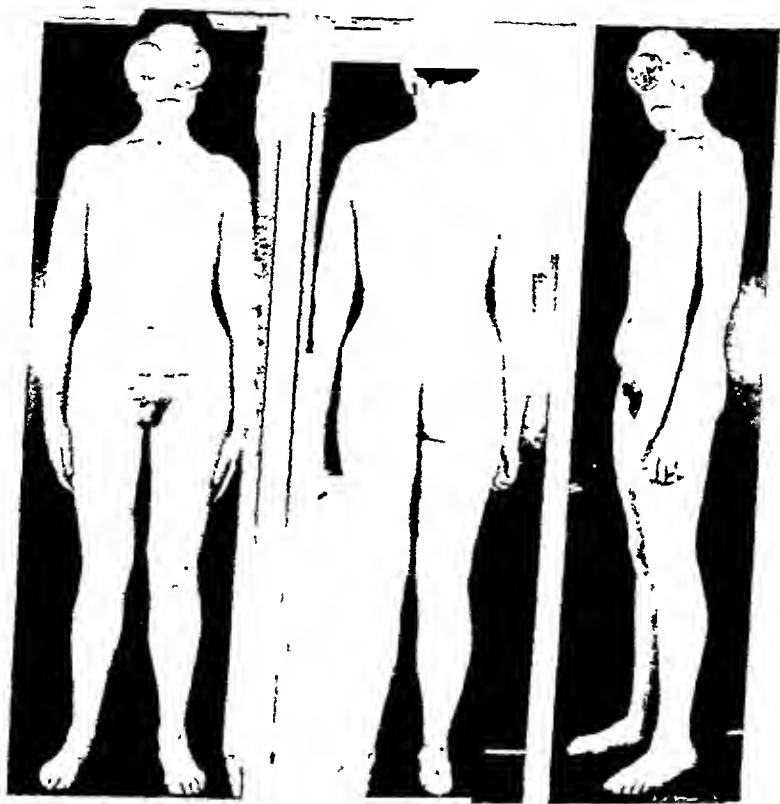
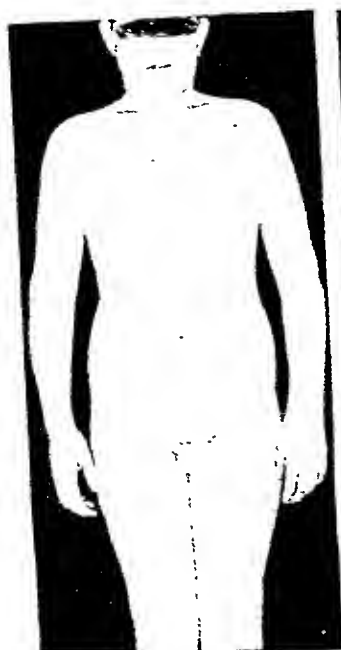
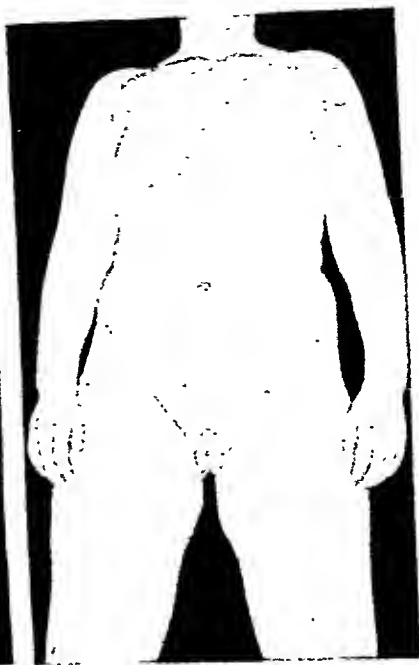


Fig. 230.—Eunuchoidism and hypogenitalism in a man aged twenty-nine years. Infantile genitalia; lack of libido and potentia, and of secondary sexual hair and beard. High pitched voice, history of obesity, weight 180 pounds at sixteen years. Deficient musculature and psychological maladjustment. Present weight 142 pounds, height  $65\frac{1}{2}$  inches. Lower measurements 35 inches, span 70 inches.

of energy and productive forces of the body. We must not disregard the other causes of hypogonadism, namely, the embryonic developmental defects that occur in true cryptorchidism and hermaphroditism, and the anatomical abnor-



Patient D



Patient F

Fig. 231.

Primary  
Hypothyroidism  
and Hypogonadism

Secondary  
Hypothyroidism  
and Hypogonadism

Patient D

Patient F

Age .....	13 years	13 years
Weight .....	151 pounds	153 pounds
Height .....	63 $\frac{1}{8}$ inches	61 $\frac{5}{8}$ inches
Lower measurements .....	32 inches	32 inches
Penis .....	1 $\frac{3}{4}$ inches	1 $\frac{1}{4}$ inches
Testes .....	1 $\frac{1}{4}$ inches	1 inch
Scrotum .....	Normal	Normal
Rugae .....	Plus	Absent
Secondary sexual hair .....	Absent	Absent
Skin .....	Dry, coarse	Soft, thin
Obesity .....	Plus	Present and regional
Thyroid .....	Small	Small

malities in the inguinal canals and in the path of testicular descent. There are also acute illnesses such as mumps and tuberculosis which are often associated with orchitis; and trauma to the testes, pathologic changes within the testes,



Patient D.D.

Patient Z.S.

Fig. 232.—Enlarged and erectile penis with major hypoplasia of the testes

	Patient D.D	Patient Z.S.
Age .....	14 years	14 years
Weight .....	68 pounds	119½ pounds
Height .....	51¾ inches	59 inches

and chronic states of malnutrition involving absorption from the intestines, such as coeliac disease and vitamin deficiencies, must also be considered in the etiology of hypogonadism. The nutritional deficiencies operate indirectly from an endocrine standpoint, since the defect is one of absorption of those chemicals required to synthesize the male hormone.

It must also be noted that *thyroid deficiency* plays a role in sexual development. Hypothyroidism also occurs in primary and secondary forms, the latter resulting from an anterior pituitary deficiency (see Fig. 231). The association of obesity in many hypogonadal cases adds to the importance of the hypothyroid condition in this disorder.

Insofar as has been determined, the anterior pituitary gonadal mechanism in the male does not have cycles of gonadotropic stimulation as is present in the female. The testes are continually stimulated by the anterior pituitary after maturity is reached. Thus, exclusive of tissue abnormality in the gonad, the first likely cause of gonadal failure in males should be sought in the anterior pituitary lobe.

# DIAGNOSIS

Since from birth onwards the male gonads are normally available for ready inspection, one can readily determine whether or not gonadal development is progressing satisfactorily even before secondary sexual features normally appear. Unfortunately, however, normal testicular development in young males is a matter of personal interpretation. Analysis of genital development in a large group of normally developing male children has not been made. The age at which specific endocrine therapy for hypogenitalism should be instituted is controversial, the present trend being to avoid early

	Patient D.D.	Patient Z.S.
Lower measurements	26 inches	31½ inches
Penis	3 inches	3¼ inches
Testes	¾ inch	½ inch
Cryptorchidism	Bilateral	Bilateral
Scrotum	Infantile	Hypoplastic
Rugae	Infantile	Present
Secondary sexual hair	No	Pubic
Skin	Normal	Normal
Thyroid	Small	Small

institution of endocrine therapy in young hypogonadal males. The opinion that therapy in young hypogonadal males should be deferred is acceptable only if we are estimating the need for endocrine therapy exclusively from the gonadal aspect. In order to arrive at a proper and complete endocrine diagnosis in a hypogonadal male during the preteen age period, a prerequisite to rational and effective endocrine therapy is the evaluation of endocrine function in terms of the body as a whole and not from the state of genital development alone.

At what age can hypogonadism be diagnosed in the male child and upon what clinical evidence shall this diagnosis be based? Since the age standards of sexual development are essentially a matter of personal and clinical experience, the clinical evaluation of the case should be made not only upon the degree of anatomical growth of the sexual organs but also upon the physiological manifestations of the hormonal output of the testes. *The size of an endocrine gland is no indication of its functional capacity*; a large, firm, insensitive testis may have a poor hormonal output. In making a diagnosis it is necessary to consider the external genital structures individually, and then as a physiological unit. In my experience, penile development is not a reliable indicator of testicular hormonal activity for I have, on numerous occasions, observed a normal or even an enlarged erectile penis associated with an unquestioned and demonstrable major degree of testicular hypoplasia (see Fig. 232). I have seen young boys and adult males with enlarged penes associated with testes the size of a very small lima bean. The state of development of the scrotum will be found to parallel more closely the size and function of the testes than does penile development. Fortunately, in the majority of cases, the hypoplasia of the testis, scrotum and penis parallel one another and the establishment of a diagnosis of gonadal hypoplasia following examination of the genital organs and the body as a whole is not difficult.

#### THERAPEUTIC INDICATIONS

I would say that the chief reasons given for consulting physicians for advice concerning the need of endocrine therapy for hypogonadism at various age levels occur as follows:

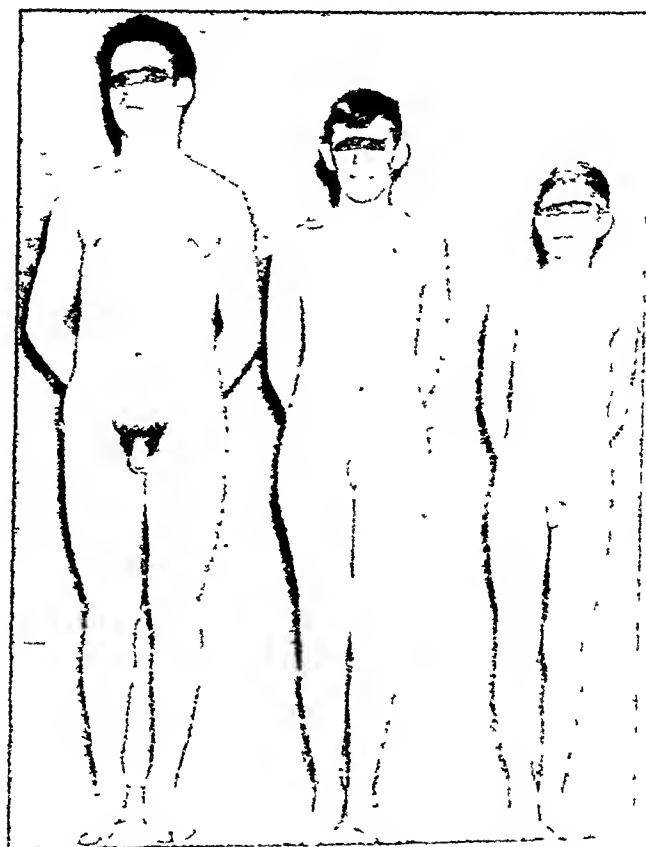
1. Cryptorchidism—from 2 years of age onward
2. Cryptorchidism and retarded growth—from 6 years onward
3. Small-sized genitalia and retarded growth—from 8 years onward
4. Obesity and hypogenitalism—from 8 or 10 years onward
5. Delayed puberty—from 12 years onward
6. Suspected hypogenitalism, sluggish maturity, psychological and associated constitutional inadequacy—from 14 years onward
7. Delayed masculinization; secondary sexual characteristics—from 16 to 25 years
8. Sterility—from 22 to 45 years
9. Male climacteric or involutional syndrome—from 45 to 65 years

In addition to these are the following pathologically induced hypogenital states which usually result in a partial or total lack of gonadal sufficiency:

1. Testicular atrophy—from 10 years of age onward—due to:
  - (a) Mumps
  - (b) Infection
  - (c) Trauma
2. Partial or total castration resulting from:
  - (a) Tuberculosis
  - (b) Chorionepithelioma
  - (c) Accidents—war wounds

The clinical manifestations of hypogonadism vary with the age of the patient. The gonadal hormone exerts its effect not only upon the primary and secondary sexual structures, but on body growth and development (Fig. 233), body metabolism, blood chemistry and physical and mental energy and mental reactions.

In the preteen age our clinical survey is confined chiefly to evidence of subnormal anatomical and physical development and a study of the metabolic status of the patient. When objective evidence of hypogonadism is found, the degree of the deficiency must be appraised. If the hypoplasia of the genitals is slight and there is an absence of constitutional and/or developmental stigmata of hypogonadism, one must recognize the importance of the authentic and accredited reports which indicate that the expectant (nontreatment) management of hypogonadism and cryptorchidism is preferable since descent of the cryptorchid testes and normalcy of the gonads have in some instances eventuated. Unfortunately, however, these reports of large groups of cases have considered the problem



Patient F. M.

Patient A. B.

Patient I. Y.



Patient F. M.

Fig. 233.—Growth—gonadal endocrinous interrelationship

purely from the genital aspect and have not set forth whether evidence of associated endocrine disorders was exhibited in the cryptorchid cases.

It is our belief that the presence or absence of clinical signs of associated endocrine deficiency should be the major point in determining whether or not one should institute endocrine therapy for cryptorchidism. If the case exhibits concomitant signs of endocrine hypofunction such as retarded growth, as well as direct evidence of hypogenitalism and cryptorchidism, the necessity for endocrine therapy, irrespective of the age period, is sufficiently established. I believe that the evaluation of the gonadal (genital) state should not be the sole determining factor of the form of endocrine therapy to be instituted. The body development as a whole, along with the general metabolic state, should determine the need, type and dosage of endocrine therapy. It has been established that defective or faulty nutrition is often a causative factor in hypogonadism, and that dietary control of abnormal nutritional states (obesity) will improve genital development in many cases. In fact, reduction of the metabolic load on the endocrine system, particularly the thyroid and pituitary glands, is an important aspect in the management of all endocrine deficiencies in which excessive food intake and obesity are present.

The preteen age patients with underdeveloped testes, complicated by cryptorchidism, are usually first referred for endocrine therapy at ages from six to eight years and upwards. To age fourteen it is usually the child's general constitutional or obese state and his retarded genital development, and occasionally mental and scholastic difficulties, which cause the parents to seek medical advice. The obesity in such cases is usually progressive in type, with a predisposition for localization of deposits in the mammary and pelvirochanterian regions. This feminine type of body contour resulting from

	Patient F. M.	Patient A. B.	Patient I. Y.
Age . . . . .	16 years	20 years	16 years
Weight . . . . .	159 pounds	111 pounds	80 pounds
Height . . . . .	68½ inches	63 inches	58 inches
Lower measurements . . . . .	34¾ inches	33½ inches	30 inches
Penis . . . . .	4 inches	2 inches	2 inches
Testes . . . . .	2¼ inches	¾ inch	1 inch
Cryptorchidism . . . . .	No	Yes—surgery	No
Scrotum . . . . .	Normal	Hypoplastic	Normal
Rugae . . . . .	Normal plus	Infantile	No
Secondary sexual hair . . . . .	Advanced	Deficient	Deficient
Skin . . . . .	Normal	Thin	Thin
Thyroid . . . . .	Normal	Normal	Normal
Gynecomastia . . . . .	Plus	Minus	Minus



the obese deposits, combined with a lack of interest, energy, aggressiveness and endurance normally exhibited by males of this age, is a prominent part of the clinical picture and the chief source of concern of the parent interested in the child's future. The state of obesity in some, the retarded growth in others, as well as the energy deficit observed in hypogonadal cases may produce profound psychological changes. The patient will often avoid the usual boyish activities, seclude himself and develop an interest in art or music, or become an ardent book lover. He avoids the normal outdoor life of other boys of his age, spending much of his time indoors.

Another factor may account for the mental and physical inertia seen in hypogonadal boys, especially those with an anterior pituitary deficiency. Not infrequently these patients, who are usually of normal or subnormal weight, have hypoglycemic attacks which vary from nervousness and exhaustion to epileptic seizures. Such patients must have supplemental therapy, such as buffer meals of fats and carbohydrates, to combat the hypoglycemia.

Medical opinion appears to favor the theory that up to age twelve nature should be allowed to take its course if retarded genital development *only* is observed. From what has been stated, however, it is evident that, irrespective of the age before adolescence at which male hypogonadism is diagnosed, the problem of therapeutic management is not one to be dismissed lightly on the assumption that the inherent natural body and endocrine forces will effect a normalization of retarded sexual development and its complications. We do not wish, however, to convey the opinion that all hypogonadal children should be treated by endocrine therapy when first observed. To do so would disregard our own clinical experience and that of others that correction of nutritional factors, particularly control and reduction of obesity, produces a beneficial effect on the associated hypogoniticism.

As the untreated hypogonadal male passes from childhood to adolescence or adulthood the endocrine and clinical picture becomes more complex; on the other hand, it becomes more clearly defined, and the objective and subjective indications for endocrine therapy are more clearly indicated as age advances. It is in the younger preteen age group that the necessity for endocrine therapy is sometimes disputed. The subject of cryptorchidism represents the contro-

versy over treatment, because here the therapist and the surgeon present conflicting records of their observations.

# ANTERIOR PITUITARY GONADOTROPINS

Anterior pituitary preparations used in the treatment of gonadal deficiency may be classified as (1) standardized and (2) unstandardized preparations.

A standardized preparation of the gonad-stimulating fraction has been obtained from the anterior pituitary lobe of cattle or sheep. This preparation is known as *anterior pituitary gonadotropin* (A.P.G.).

*Polyansyn* is a preparation containing all the anterior pituitary fractions (tropines), in the proportion said to exist in the anterior pituitary gland. It finds its use in cases in which there are general clinical signs of anterior pituitary deficiency coexisting with gonadal deficiency. A.P.G. is classified as

## ANTERIOR PITUITARY GONADOTROPINS

Preparation	Dosage
<i>Anterior Pituitary Gonadotropic Extract</i> (1 cc. = 300 units) Ayerst, McKenna & Harrison, Inc. Armour	1 cc. daily or every other day or 2 cc. every other day until 30 cc. are administered. (Continuous administration of this preparation is likely to produce an antihormone state.)
<i>Polyansyn</i> (1 cc. = 25 units) Ayerst, McKenna & Harrison, Inc. Armour	Same as above.
<i>Prephynin</i> (1 cc. = 100 units) Stearns	1 or 2 cc. every other day for three months.
<i>Arifonin</i> (1 cc. = 50 R.U. gonadotropin and 200 guinea pig units thyrotropin) Roche-Organon, Inc.	1 cc. two or three times a week. (Because of thyrotropic content check pulse and basal metabolic rate.)

a gonadotropin along with two other gonad-stimulating preparations which while not derived from the anterior pituitary lobe have biological actions on the gonads which closely approach those observed with anterior pituitary gonadotropin.

A more recent preparation of this gonadotropic class is *pregnant mare's serum gonadotropin* (P.M.S.). The biological action of P.M.S. more closely approaches that of the anterior pituitary gonadotropin than either the anterior pituitary-like factor (A.P.L.) or chorionic gonadotropin.

The unstandardized anterior pituitary preparations are solutions of anterior pituitary lobe and the dry extracts of the same. Their therapeutic value has been determined only by clinical trial; accordingly, their therapeutic value is questioned and their use is considered unscientific by many. While numerous clinically experienced endocrinologists advocate their usage on the basis of results obtained in animal experiments, their usage in the human has failed to confirm the findings.

#### CHORIONIC GONADOTROPINS

The chorionic gonadotropins have been most widely used in the treatment of *cryptorchidism and hypogonadism*. The dosage has varied widely from 100 rat units to more than 1000 rat units from daily to three times a week and for periods of two or three months to years. As one dosage level has failed to effect results in cryptorchidism, it has been the custom for some clinicians to raise both the dosage and the frequency of administration. The same therapeutic regimen has been resorted to in testicular underdevelopment. This accounts for the wide range of dosage utilized in these disorders. In both types of cases there has been a high percentage of failures and, to a lesser degree, abnormal penile growth and advancement of skeletal and body maldevelopment.

We believe that chorionic gonadotropic therapy is best suited to cases of cryptorchidism which persist to the age of twelve to fourteen years, in which delay in pubertal reactions is manifest. From 500 to 750 rat units are administered by hypodermic three times a week for a period of eight to twelve weeks. If descent does not occur one month after terminating the first series, surgery should be considered if there is a possibility that an anatomical obstruction is a cause of the cryptorchidism, otherwise a second series is instituted. If this fails, surgery is definitely indicated. When a single

# CHORIONIC GONADOTROPINS

## PLACENTAL OR URINARY EXTRACTIVES

<i>Preparation</i>	<i>Dosage</i>
<i>A. P. L.</i> (1 cc. = 100 or 500 R.U.) Ayerst, McKenna & Harrison, Inc.	100-500 R.U. daily or every other day.
<i>Antuitrin S</i> (1 cc. = 100 or 500 I.U.) Parke, Davis & Co.	Same as above.
<i>Pregnyl</i> (1 cc. = 100 or 500 I.U.) Roche-Organon, Inc.	Same as above.
<i>Pranluron</i> (1 cc. = 150 or 750 I.U.) Schering Corp.	150 to 750 I.U. three times weekly.
<i>Follutin</i> (1 cc. = 100 or 500 I.U.) Squibb	50 to 1000 I.U. three times a week.
<i>Kerctin</i> (1 cc. = 100 R.U.) Winthrop	100 to 500 R.U. three times a week.

## PREGNANT MARE SERUM EXTRACTS

<i>Anteron</i> (1 cc. = 400 or 2000 I.U.) Gonadotropic Schering Corp.	400 I.U. three times weekly for two to three months.
<i>Gonadogen</i> (1 cc. = 200 or 400 I.U.) Gonadotropic	400 to 1200 I.U. as indicated.
<i>Gonadin</i> (1 cc. = 500 I.U.) Gonadotropic	250 I.U. three times weekly. 500 to 1000 I.U. weekly.

undescended testis is extremely small and the other testis in the scrotum has undergone compensatory hypertrophy, puberty may be progressing satisfactorily and surgery is not so imperative. Since the blood vessels to hypoplastic testes are also small they are likely to be damaged during operation or by postoperative healing, and atrophy of the testes may occur. In favor of surgical intervention, on the other hand, even when the cryptorchid testis is suspected to be very small, is the increased incidence of malignancy reported to occur in cryptorchid testes which are intra-abdominal.

*Pregnant mare serum* is another gonadotropic factor now available for stimulating gonadal development. This preparation and the *gonadotropic factor obtained from the anterior pituitary lobe* have not in our clinical cases produced favorable responses.

#### ANTERIOR PITUITARY-THYROID THERAPY

We continue to rely upon the therapeutic activity of anterior pituitary extract administered orally, in hypogonadism in male children. As a general rule we prescribe a daily dose of 1 grain of anterior pituitary extract for each four years of age. Thyroid U.S.P. is combined with the anterior pituitary extract in the proportion of 1 grain of thyroid to 10 grains of anterior pituitary, when signs of hypothyroidism coexist. When calcium is required we administer calcium glycerophosphate, 4 to 8 grains daily, in combination with the above. While this method of therapy does not effect as rapid a therapeutic response as might be desired, it is more acceptable to young boys and can be adjusted as progress is observed.

The time of administration of oral anterior pituitary extract is all important. It should be administered after meals. The animal glandular extract should be given all the advantages of extraction by the juices required for the digestion of the animal food we ingest. If the anterior extract is not administered at or near the conclusion of the meals it is *relatively inactive*.

No specific effect of therapy is observed during the first three months of therapy, but from a general constitutional stand-

point the patient observes an increase in energy and physical activity. Later, a genital response to therapy is evident in an increase in pubic hair, an improved appearance and increase in size of the scrotum and a gradual increase in size of the penis. After four and one-half to five months of therapy an increase in the size of the testes occurs, averaging roughly  $\frac{1}{4}$  inch for every six months of therapy.

At the end of six months' therapy one observes a generalized stimulation of hair growth, axillary hair growth usually first appearing at this time. The high pitched voice begins to deepen but cracks occasionally. During the period of six months when the improved genital development is occurring a concurrent stimulated and often an accelerated normal statural growth occurs. Improved muscle development also appears. This improvement in genital and physical development tends to stabilize the psychological reactions, the total effect therefore being to normalize the maladjusted young hypogonadal male.

Therapy can usually be reduced in about two years, and concluded as a normal rate of development is reestablished. It should be remembered that the natural endocrine forces do not rapidly effect sexual maturity and there is, therefore, no reason in young males to effect by endocrine therapy an abnormally rapid development of sexual function.

The effect of orally administered anterior pituitary extract and thyroid to young hypogonadal males has been studied in over 100 private and clinic cases, which have exhibited the following signs of gonadal deficiency: (1) retarded development of all the genital organs; (2) persistence of puerile voice pitch; (3) retarded or absence of secondary sexual hair; (4) deficient extremity hair growth; (5) deficient body musculature and hypotonia; (6) deficient physical energy; (7) defective psychological advancement; (8) immature male personality; and (9) growth dyscrasia; disproportion of the trunk and total height ratio.

The following case histories serve to illustrate the results that are usually obtained when the above therapy is administered to well defined cases of male hypogonadism.

The eldest of four brothers (Case 1) was referred for examination at the age of thirteen and one-half years with all the complaints enumerated above. The length of his penis and testes in their longest diameter was  $1\frac{1}{2}$  inches and  $\frac{3}{4}$  inch respectively. The scrotum was poorly developed and its rugae were deficient and underdeveloped. His initial therapy was anterior pituitary extract, grain  $\frac{1}{2}$ , and thyroid, grain  $\frac{1}{10}$ , three times a day, administered at the end of each meal.

Improvement under this therapy, which was continued for a long period, was marked, but unfortunately the patient contracted mumps complicated by an orchitis which induced a second period of retarded gonadal development. In our opinion, the orchitis of mumps has a devastating effect upon the testis structure and particularly upon its hormonal capacity.

In spite of the fact that the testes of the patient had developed to normal size after five and one-half years of therapy, he proved to be no exception to the general observation that mumps causes an intrinsic tissue change in the testes which interferes with male hormone production even if atrophy of the testes does not occur. Evidence of diminished male hormone output from his normal-sized testes is shown by the failure of his penis to develop to normal adult size, the failure of his voice pitch to become normal, and certain of his mannerisms which are at least submasculine. His pubic, axillary and body hair growth are normal but there is a deficient beard growth. However, the therapeutic end-result is better than that of an adult male, who, after attaining genital normalcy, contracts mumps and orchitis, since experience has shown that this patient is more reactive to testosterone therapy than the latter.

The effect of therapy upon growth and upon the testes in Case 1 is shown graphically in Fig. 234. Each of this patient's three younger brothers (Cases 2, 3 and 4, Fig. 234) manifested retardation of growth and genital development at puberty. As will be seen from the chart, patients 2 and 3 were allowed to establish definite physical evidence of retarded growth and genital development before therapy was instituted. As the familial or inherited anterior pituitary deficiency became apparent the fourth brother was treated earlier than the others. A more rapid effect of therapy became evident in this case within three months after instituting it. Citations of improvement of symptoms and details of therapy in these cases would be repetitious. Patients 2, 3 and 4 were started on the same therapy as the first patient. The maximal daily dosage of anterior pituitary extract administered orally was 4 grains, with an average dose of 2 grains. None of these boys showed a tendency towards obesity; accordingly, their average daily dosage of thyroid was  $\frac{1}{2}$  grain and the maximal dosage was  $\frac{1}{2}$  grain. They all have matured sexually, except

as noted above in Case 1. In the other brothers the secondary sex characteristics, voice, body hair development progressed

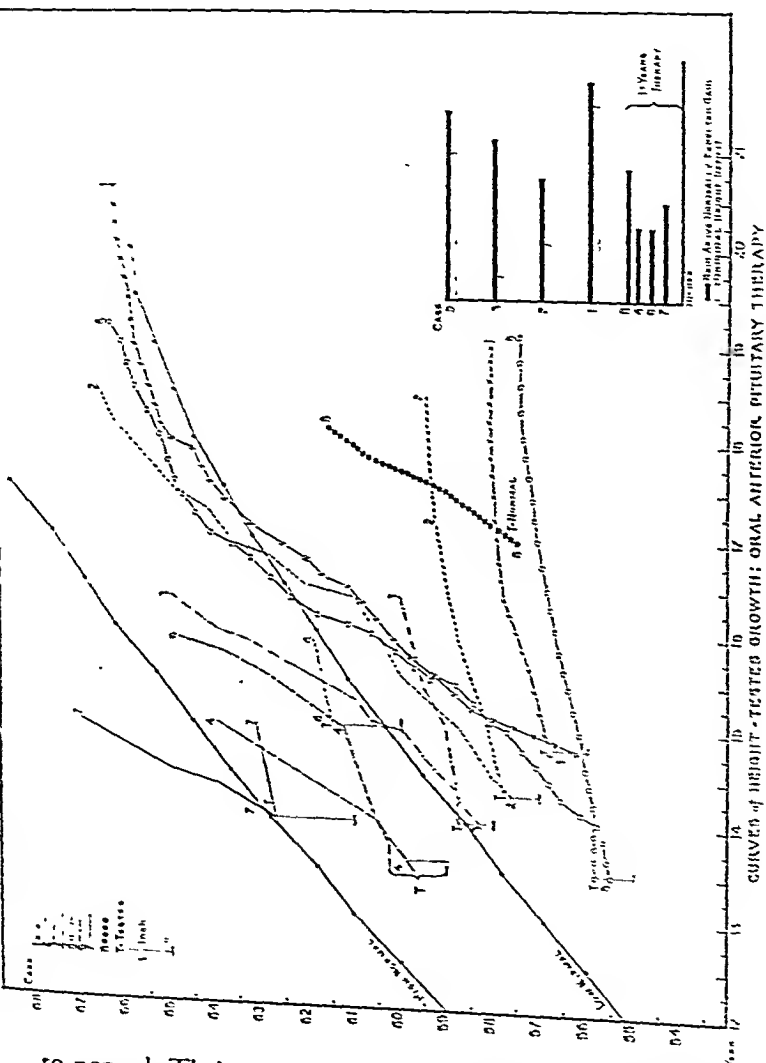


Fig. 234.

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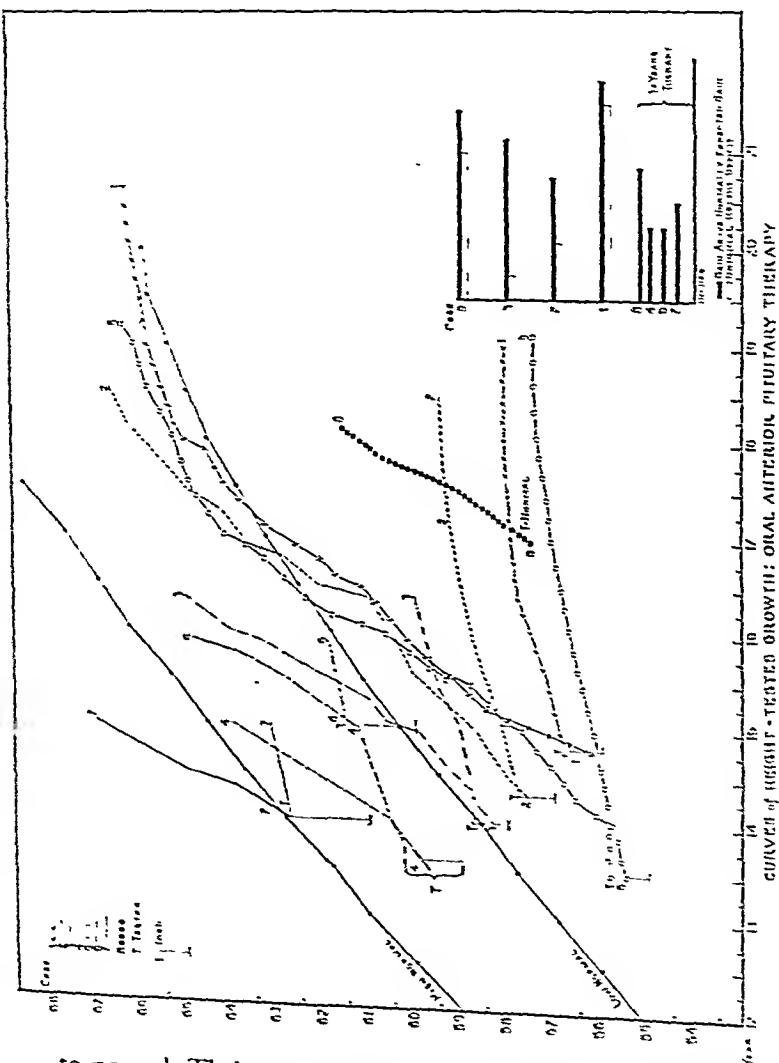


Fig. 234.

to normal. Their testes developed to normal dimensions, i.e., 2 to 2½ inches in their long diameter, and are of normal shape and sensitivity. Their scrotums are well developed and

their penes are normal size—4 to 4½ inches long in a relaxed state. They are normal, physically and psychologically. All have exhibited an accelerated growth rate and all have attained normal height as is shown in the chart.

The chart (Fig. 234) also includes the graphs of the statural and testicular growth produced by oral anterior pituitary therapy in nonbrothers who presented the hypogonadal syndrome herein described. These individual graphs demonstrate a consistent, concomitant growth-stimulating effect on both the gonads and stature. Patient 5 was referred because of retarded growth and genital development. All members of his family are short in stature. He is now taller than the other members of his family and his genital organs are well above the normal average. Patient 6 was referred because his rate of growth and attained height and genital development were estimated to be inadequate for subsequent admission to a military service school. The response to therapy here was very satisfactory staturally, genitally and mentally. In fact he was able to enlist in a foreign service. Patient 7 exhibited a marked genital response to therapy. He had a moderate degree of genital hypoplasia, with the chief symptoms being rapid gain in weight, typical localized obesity deposit in the mammary, abdominal and pelvotrochanteric regions, physical and mental lethargy, and psychological maladjustment. Following the daily administration of from 2 to 3 grains of anterior pituitary extract and ½ to 1 grain of thyroid his weight gain was controlled and reduced, sexual development progressed rapidly and the sexual hair increased to normal and the voice deepened to a husky pitch. Therapy was discontinued at the age of fifteen and one-half years. His sexual progress has been satisfactory to the point that the hair growth on his upper lip and beard regions is distinctly evident.

The criticism might be offered that the increases in height and the genital development in our cases might have occurred normally without therapy. Our experience is quite to the contrary. We observe that the interruption of therapy or its discontinuance is associated respectively with a lag or cessation of therapeutic effect. Interruption of therapy has been practiced in our cases and the lag of growth effect is observed in the graphs in Cases 1 to 4.

Case 8 is included in the graph to show the marked effect of anterior pituitary therapy on growth in a patient with normal sized testes and penis, and secondary sex hirsutism. He was markedly retarded in growth. His chief complaints were severe daily headaches, inability to gain weight, high pitched voice and lack of physical and mental energy. The prompt therapeutic results, subjective and objective, proved that a male hormone deficiency existed.

The case of G. S. illustrates points concerning the duration and continuance of therapy. He was referred at twelve and one-half years of age with a history of having completed a series of antuitrin S injections, 2 cc

twice a week for a period of ten weeks, with negative results on his hypoplastic testes. These were the size of the average olive pit and the penis was  $1\frac{1}{4}$  inches long. The scrotum was underdeveloped. He was given 6 grains of anterior pituitary extract and  $\frac{1}{2}$  grain of thyroid daily for four months. When testicular growth was established the dosage of anterior pituitary extract was reduced to 4 grains. Satisfactory progress was maintained and at the end of two and one-half years the anterior pituitary thyroid therapy was temporarily discontinued since a normal genital development for the patient's age had been reached. His physical and psychological states were satisfactory.

The patient did not return for one year, and during this period he received no therapy. He returned at age sixteen and one-half years because he had failed to maintain genital development and was gaining weight rapidly and becoming introspective and shy. Examination revealed that his penile and testicular measurements were practically the same as a year previously, namely, 3 inches and  $1\frac{1}{2}$  inches respectively. Therapy was resumed at the initial dosage. Hypogonadal cases must be maintained under observation until full genital development and normal male hormone secretion are assured.

We do not hold the opinion that it is desirable to maintain *continuous* oral endocrine therapy in young hypogonadal males. On the contrary, we believe in interrupting therapy or at least reducing dosage by 50 per cent every three to six months to determine the effect and need of therapy. Furthermore, we are generally opposed to the administration of endocrine preparations in large dosage; in fact, we attempt to thrust all the load we can on the patient's own endocrine mechanisms. If we maintain the dosage of the endocrine preparation in excess of the patient's endocrine deficiency we will eventually increase this deficiency, since we remove the normal demand stimulus upon the endocrine gland.

The dosage, type and duration of therapy cannot in fact be standardized. It must be individualized and selective; and last but not least, it must be rationalized to the physiological needs of the body. Failure to do this and shotgun therapy account for the majority of therapeutic failures in young hypogonadal males. It also permits the opinion of the anti-oralists to survive.

This form of therapy is effective in at least 70 per cent of our cases. There have been some complete failures observed. Failure can usually be foreseen in those cases in which the testis is extremely small (infantile) and its form and shape, as determined by palpation and measurement, is that of a small

lima bean, with the consistency of a fibrotic tissue having a thick capsule. Digital pressure on this testis does not produce a sense of discomfort to the patient. All methods of therapy aimed at activating the testes in such cases have failed, but the male hormone, testosterone, has in such instances corrected the male hormonal deficiency.

### TESTOSTERONE (MALE HORMONE) PREPARATIONS

<i>Preparation</i>	<i>Dosage</i>
<i>Oreton</i>	
(5, 10, 25 mg. testosterone propionate per 1 cc.) Schering Corp.	Oreton—adult males: 25 mg. three times a week, reducing gradually to 20 mg. as control of deficiency is established. Adolescent males 5 to 10 mg. every three to seven days Oreton M—three to five times the above dosage.
<i>Neo-Hombreol</i>	
(5, 10, or 25 mg. testosterone propionate per 1 cc.) Roche	Neo-Hombreol—5 to 50 mg. weekly according to the indications Neo-Hombreol M—20 to 50 mg. weekly
<i>Perandren</i>	
(5, 10, or 25 mg. testosterone propionate per 1 cc.) Ciba	Perandren—dosage varies with the clinical syndrome and age of patient—5 mg. to three 25 mg. doses per week Metandren—same.
<i>Oreton M</i> —Schering <i>Neo-Hombreol</i> —Roche <i>Metandren</i> —Ciba	These preparations are methyl testosterone dispensed as 10-mg. tablets

### OINTMENTS

<i>Oreton F</i> —Schering (2 mg. testosterone per applicator) <i>Neo-Hombreol</i> —Roche (4 mg. testosterone per dosule) <i>Perandren</i> —Ciba (2 mg. testosterone propionate per grain of ointment)	The ointments are applied locally to the inguinal and genital regions every night or every other night as required. They are best suited for local growth stimulating effect and maintenance dosage.
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### TESTOSTERONE (MALE HORMONE) THERAPY

Testosterone (male hormone) has been determined to be the hormone produced by the testes. The clinical results obtained with the various preparations of testosterone in gonadal deficiency in the human have confirmed the results obtained by animal experimentation. Testosterone is a chemical substance, closely related in chemical structure to the adrenal cortical and the ovarian hormones, estrogen and progesterone.

It is rapidly broken down into biologically less active male hormone substances such as androsterone; and it has been found necessary to combine with it certain acid radicals, as the propionate, to prevent its too rapid utilization.

Testosterone preparations in various chemical combinations—testosterone propionate, methyl testosterone—when administered cause a disappearance of the clinical signs and symptoms of gonadal deficiency, irrespective of the age of the patient. Testosterone does not stimulate gonadal development but corrects the male hormone deficiency by acting as a replacement agent. Only the gonadotropins are biologically capable of stimulating gonadal development, thus indirectly increasing male hormone production. In the ideal therapeutic regimen in gonadal deficiency associated with hypoplastic gonads they are first given a trial.

The result of male hormone administration after failure of anterior pituitary or gonadotropin therapy is illustrated in patient H. H. At the age of sixteen years this boy showed delayed growth and genital development and absence of secondary sex characteristics. Equally prominent were his shyness, the embarrassment caused by his high pitched voice, the consciousness of his infantilism and the resultant psychological disturbance.

At the time of examination he was 56 inches tall and weighed 74½ pounds. During the preceding year he had received interrupted anterior pituitary-thyroid therapy without sufficient improvement of the genital hypoplasia and secondary sex characteristics to satisfy him. Because of his increasing concern he was given 10 mg. of Oreton M orally every other night. The therapeutic response was very satisfactory at the end of one month of therapy. He continued to improve in weight, height and energy as therapy was maintained. The mental improvement was particularly noted as soon as the penis enlarged, the pubic hair became heavier and darker and the voice pitch deepened. He lost the feeling of embarrassment that had haunted him and gained confidence in himself. At the end of eight months, during six of which he received Oreton M therapy, he was 60½ inches tall and weighed 94 pounds. The secondary sex characteristics were fully developed and the penis was of normal size. The testes and scrotum showed increased development. His voice deepened beyond normal pitch but is rising to nearly normal pitch two months after discontinuing therapy.

Another patient, aged sixteen years, similarly treated during the same period, was 55½ inches tall and weighed 76 pounds when first seen. After six months of Oreton M therapy his height increased to 58½ inches and his weight to 83 pounds. He had a corresponding improvement in genital development and normalization of secondary sex characteristics.

In these cases there is exhibited not alone the growth effect of male hormone on genital and associated secondary tissues

but equally its somatic growth effect on osseous and protein tissue, particularly muscle tissue. The weight gain which occurs during male hormone therapy is not due to deposition of fat tissue but is chiefly derived from increased muscular development. Because of the increased musculature, better physique, and the increase in physical and mental energy, the patient's whole personality will change completely and he will assume a normal place, physically and mentally, in the activities of his own age group.

Male hormone therapy should be adjusted to produce a balanced physiological response in the patient. The advancement of the sexual hypoplasia and secondary sexual characteristics to a normal state is not the only objective to be sought. Our purpose is also to normalize the patient's constitutional and psychological reactions. In young males the excitation of libido must be carefully watched and the dosage of testosterone regulated to control this psychosexual reaction. The act of masturbation may be incited by the rapid penile growth and prolonged erections produced by excessive therapy.

In the pre-adult ages, for social reasons alone, it is more desirable to effect a *gradual* rather than a rapid compensation of the male hormone deficiency by the administration of male hormone. A priming dosage of 10 to 25 mg. of testosterone propionate weekly is given before the patient is allowed to experience the total effect of sexual excitation and erections. Evidence that a priming effect has been obtained is seen in the psychological improvement, the weight gain and increase in energy.

This progressive therapeutic regimen is particularly applicable in hypogonadism in males between the ages of sixteen and twenty-five years.

In this age group we find a large number of eunuchoids who have experienced neither libido nor potentia. Symptoms of physical and mental inertia are frequently a major complaint. Scholastic or business progress is often unsatisfactory because of lack of drive and endurance. Some patients lack inspirational effort and realize they are misfits economically, socially and maritally. It is in this group of cases with ad-

vanced hypogonadism that one observes the full therapeutic value of male hormone therapy. From 10 to 25 mg. of testosterone propionate is given two to three times weekly to overcome the syndrome of sexual deficiency.

Advanced hypogonadism in the age group under discussion is similar in its constitutional and mental effects to the *male climacteric*. The latter has the added symptoms of flashes, sweats, irritability, depression, headaches, loss of libido and diminished or absent potentia. The climacteric male has been sexually competent though he has regressed to a sexual state comparable to the hypogenital patients (excluding the eunuchoids) of the twenty-year age group. The cause may have been a long illness, prolonged mental strain, testicular atrophy after mumps, tuberculosis, or other infection, or trauma of the testes which has damaged their function.

The therapy of both the male climacteric and of hypogonadism in sixteen-to-twenty-five-year-old males is essentially similar: 25 mg. of testosterone propionate is given two to three times a week until the desired clinical results are obtained.

In the climacteric age group one finds patients with a prior history of mumps who are refractory to testosterone therapy. The dosage in these cases has had to be doubled and even quadrupled before libido and partial potentia have been stimulated. One might believe the loss of libido and potentia to have a psychological basis were it not for the fact that these patients experience return of the energy, initiative, aggressiveness and the normal mental reactions they formerly possessed. They again become physically and mentally fit for economic and social life. This return of self-confidence and vigor is so gratifying and satisfying that the diminished libido and potentia are of minimal concern to the patient.

The best form of testosterone therapy for the *eunuchoid* is the *implantation of pure testosterone* in dosage of from 300 to 450 mg. per implant. The dosage is judged by the patient's response to hypodermic therapy. Implantation therapy permits the gradual absorption of testosterone from the pellets. The absorption from such an implant has been estimated by us to be from 3 to 5 mg. per diem. As the implant is ab-



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sorbed, the therapeutic response diminishes. The effect of an implant of from 300 to 450 mg. of testosterone usually disappears in from three to four months.

The genital tissues of the eunuchoid appear to be naturally primed to testosterone therapy, for here we observe a most rapid and effective response to testosterone in all phases of biological and physiological reaction. Erections have appeared for the first time as early as thirty-six hours and for as long as ten days after implantation, when implantation has been the initial therapy. There follow the constitutional effects of weight gain, muscular development and increased energy; and the appearance of a more aggressive masculine personality. The genital organs develop, secondary sexual characteristics appear and progressively develop and the voice deepens in tone. Extremity hair appears and subsequently facial hair growth occurs. As the therapeutic effect continues, a rehabilitation of a patient becomes evident, because he loses his "misfit" attitude.

Most eunuchoids treated with 300 mg. implants exhibit a definite and slow but progressive development of the testes, after two years of therapy with an average of six implants. At this rate of progress it will take at least five more years of therapy to develop the testes to normal size.

This therapy is purely substitutional and corrects a chronic deficiency state. It must be carried on indefinitely or until such time as a definitely active gonadotropic preparation for treating males is found. The chorionic and other gonadotropins have failed to develop the testes in true eunuchoidism.

Testicular development has also occurred with *methyl testosterone* orally administered in 10-mg. dosage daily or every other day, and also when the *inunction of testosterone* has been administered to hypogonadal children or youths in whom arrest or retardation of statural growth is present. In these cases growth stimulation also occurred. No adequate explanation can be advanced to account for the testicular growth phenomena observed in these and the eunuchoid cases unless we postulate that it is a synergistic effect on the testes of an accelerated growth hormone effect and a *slow absorption* of the testosterone secured by these methods of administration.

Both the eunuchoids and the growth stimulated hypogonadal patients have had a supernormal growth curve. Unfortunately *the size of the testis is not an indicator of its hormonal capacity* and to date there is no clinical evidence that the improvement in size of the testes observed in our eunuchoid cases has diminished the requirements for testosterone therapy.

The effectiveness of male hormone therapy in *sterility* is limited to those cases in which the male has viable sperm but is impotent. All evidence indicates that testosterone depresses spermatogenesis. Thus, while therapy improves one fault it establishes an equally important factor in sterility. The advisability of its use in sterility must be individually evaluated.

*Castrates* rapidly respond to the oral administration of Oreton M, 10 to 20 mg., given on retiring. When therapy is instituted even in the height and severity of their symptoms they obtain relief from the severe flashes and sweats in about five to seven days. Libido and potentia return, physical and mental energy returns to normal, and the depressed and irritable state of mind disappears. The administration of stilbestrol and hexestrol has relieved the hot flashes and profuse sweats experienced by the castrate; but it does not affect the loss of libido or potentia nor the loss of physical or mental energy or their psychological distress. The implantation of testosterone is the ideal form of therapy for the surgical castrate.

In advanced testicular hypoplasia with constitutional inadequacy and psychological maladjustment in the pubertal age, 10 mg. of Oreton M may be given initially every other night, and later nightly, until the boy becomes better readjusted. During this period the anterior pituitary-thyroid therapy is also given. As the patient improves testosterone therapy is gradually withdrawn and the anterior pituitary-thyroid therapy is continued as long as required.

From the ages of twelve to sixteen years the hypogonadal male experiences the psychological effect of his sexual subnormality. Some boys react more than others and whenever one suspects by reason of the patient's behavior a suppressed state of psychological disturbance as evidenced by unmasculine in-

sorbed, the therapeutic response diminishes. The effect of an implant of from 300 to 450 mg. of testosterone usually disappears in from three to four months.

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4. The therapeutic problems involved in gonadal deficiency are related, not only to the development state and the hormonal capacity of the gonads, but also to the general constitutional and psychological state of the patient, and the physiological state and hormonal capacity of the endocrine system as an interrelated physiological mechanism.

5. In our hypogonadal cases the gonadotropins have been ineffective in the treatment of testicular hypoplasias. In most pre-adult males we have found that the oral administration of anterior pituitary extract combined with small doses of thyroid extract is a more reliable method of treating testicular hypoplasia and the associated hypogonadism.

6. Testosterone therapy is a specific therapy for hypogonadism in young adult males whose psychological maladjustments are the result of testicular deficiency; in eunuchoidism, and in the male climacteric. In impaired or absent libido and impotentia, testosterone therapy produces results which are often but not consistently favorable. Negative results are most frequently observed in cases in which a mumps orchitis preceded the onset of symptoms.

7. In our experience, mumps has a most devastating effect on testicular structure and function. It results in atrophy of the testes and penis and the production of a male hormone deficiency syndrome of a minor or major degree, which persists over a period of years.

terests, it is usually required that a more intensive male hormone therapeutic program be initiated. This is best obtained by the hypodermic administration of testosterone propionate in 10- to 25-mg. doses every three to five days and for about eight to twelve injections. When the therapeutic effect of male hormone is observed by the patient, his confidence is obtained and oral male hormone therapy can be used.

While testosterone therapy in males is indicated in cases of testicular deficiency, it should be limited or withheld from those patients in the advanced ages in whom increased physical energy and an increase in sexual reactions may unfavorably affect their cardiac reserve.

The oral preparation, methyl testosterone, has only from one-third to one-fifth the activity per milligram of injected testosterone propionate.

Testosterone administered by inunction is extremely slow in producing its effect as compared with other methods of administration.

Testosterone by implant is the most effective and economical method of treating the eunuchoid or the castrate.

#### SUMMARY

1. Hypogonadism, an endocrine disorder, results from a partial or total deficiency of testosterone secretion by the testes. The defect in testicular function may result exclusively from abnormalities or pathologic changes within the testes and is designated as primary hypogonadism; or from partial or total failure of the anterior pituitary lobe to produce its gonadotropic factor, and is designated as secondary hypogonadism. Thyroid deficiency may also play a role in this latter type.

2. In primary hypogonadism the testicular function per se is only involved. In secondary hypogonadism the primary endocrine deficiency is in the anterior pituitary and/or in the thyroid, and the testes are secondarily involved.

3. The gross clinical picture of hypogonadism varies with the age of the patient, owing to the fact that growth, metabolic, developmental and psychic reactive processes are influenced by testosterone deficiency.

## ENDOCRINE SYNDROMES DUE TO LESIONS OF THE CENTRAL NERVOUS SYSTEM\*

ERNEST A. SPIEGEL, M.D.†

ORGANIC as well as functional diseases of the central nervous system may produce true or apparent endocrine syndromes in various ways. In one group endocrine glands receiving impulses from the central nervous system may be influenced in the direction of hyperfunction or of hypofunction; *e.g.*, diseases of the subcortical ganglia may induce signs of hyperthyroidism, and psychogenic inhibition of the anterior lobe of the pituitary may cause a picture somewhat similar to that of Simmonds' cachexia. There is also the possibility that a central lesion may influence the function of an endocrine gland indirectly, without using direct nervous pathways. For instance the activity of the gonads may be affected by a hypothalamic disease that influences the function of the pituitary and the production of its gonadotropic hormone in particular.

Another group is represented by cases in which endocrine symptoms are imitated by diseases of the central nervous system. Since the brain is the effector organ upon which certain hormones act, disturbances in its function may be caused by certain endocrinopathies; *e.g.*, irritative motor phenomena in parathyroid insufficiency. However, somewhat similar clinical pictures may be produced by the action of other agents on the brain, as will be pointed out later in more detail.

Finally, so-called trophic disturbances appearing in the course of chronic nervous diseases may bear a certain resemblance to trophic disorders of endocrine origin. *E.g.*, in syringomyelia an abnormal enlargement of the hands and

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(Myerson and Berliner<sup>7</sup>) or carbon dioxide poisoning (Vanotti<sup>8</sup>) may produce symptoms of hyperthyroidism.

In analyzing the mechanisms of such cases of hyperthyroidism of centrogenic origin, one has to bear in mind that the hypothalamus may act upon the thyroid not only by way of the cervical sympathetic but also by influencing the output of the thyrotropic hormone of the anterior pituitary. In certain instances this latter mechanism may be even more important than the former. This is shown by the experience that section of the stalk of the pituitary is able to prevent the stimulation of the thyroid that normally occurs on exposures to cold, while bilateral cervical sympathectomy does not have such an effect (Uotila<sup>9</sup>).

#### PARATHYROID INSUFFICIENCY

There exists no proof that the functional state of the parathyroids may be influenced by impulses originating in the central nervous system. Various nervous disorders may, however, imitate some motor manifestations of tetany. *Hysterical attacks* may mimic the convulsions seen in tetany; the picture will, however, usually be more variable, and an examination in the intervals will fail to reveal the typical signs of overexcitability of nerves and muscles as well as an abnormally low calcium level in the blood. It seems advisable, however, to be rather careful in the interpretation of isolated signs of overexcitability. An isolated Chvostek sign may, for instance, be found in hysteria or in tuberculous patients, and a sign such as the Trousseau phenomenon may be easily imitated. In the true Trousseau sign there usually is a definite latent period between the compression of the nerve and the appearance of the muscular spasm; one should therefore be suspicious if the spasm appears immediately following the application of pressure on the arm.

A careful history with a consideration of the conditions under which the convulsions appear is, of course, very important. One must bear in mind that psychic trauma also may occasionally precipitate spasms in tetany. Finally, a combination of hysteria and tetany may occur, and a hysterical hyperventilation may precipitate an attack of tetany.

fingers may develop that may mimic to a certain extent the changes observed in acromegaly.

In the following survey the above possibilities will be discussed as they apply to the various endocrine syndromes.

### HYPERTHYROIDISM

The nerve fibers supplying the thyroid seem to have chiefly a vasomotor function, while a secretory function has not been proved with certainty. Chronic faradic stimulation of the cervical sympathetic may, however, increase the size and colloid content of the respective half of the thyroid (Reinhardt<sup>1</sup>). This suggests that a dysfunction of this gland may, in certain cases, be caused by disturbances in its innervation. In fact Dr. Adolf and I<sup>2</sup> were able to find chronic mononuclear infiltration of the upper cervical ganglion and of the cervical sympathetic in two cases of exophthalmic goiter.

Thus there seems to exist a certain group of cases in which the irritation of the cervical sympathetic may play a primary role. Laignel-Lavastine and Bloch<sup>3</sup> once observed a patient with exophthalmic goiter that was apparently caused by the stimulation of the cervical sympathetic by a postpleuritic fibrosis of the pleura about the apex of the lung; and Curschmann<sup>4</sup> described a tabetic woman with intermittent symptoms of exophthalmic goiter that appeared simultaneously with gastric crises. The influence of the higher centers upon the activity of the cervical sympathetic is demonstrated by the studies of Karplus, Kreidl, Einthoven and Hoogerwerf,<sup>5</sup> who recorded an increase in the electrical discharges of the sympathetic on stimulation of the hypothalamus. Furthermore, that one of the most cardinal manifestations of thyroid activity, the basal metabolic rate, may be influenced from the central nervous system was demonstrated by the fact that hypothalamic lesions induce a considerable drop of this rate (Grafe and Gruenthal<sup>6</sup>). Clinically it is an old experience that psychic trauma may precipitate the outbreak of exophthalmic goiter, and that the course of this disease may be made worse by emotional upset. But there are also experiences showing that more or less localized organic diseases of the subcortical ganglia such as produced by encephalitis

eases (e.g., typhoid fever, pneumonia). In such cases the fever and disturbance of consciousness are, of course, due to the precipitating disease. Diagnostic difficulties may arise also in cases in which occasional epileptiform convulsions are the only after-effect of a *birth injury*; besides a careful history and complete neurologic examination, encephalography may help to detect the brain injury. *Poisons* that affect the central nervous system may on the one hand produce symptoms simulating tetany; on the other hand they may change a latent into a manifest tetany, if there is a relative insufficiency of the parathyroids, as shown by experiments on animals in which only a part of the parathyroids was extirpated (Rudinger<sup>11</sup>). This should be considered in cases of lead poisoning. Guild<sup>10</sup> mentions that infants in the age of active teething often chew paint from cribs and toys and may develop signs of lead encephalopathy that may simulate the convulsions of tetany. The possibility should, however, be borne in mind that in a part of such cases lead poisoning and relative parathyroid insufficiency may combine in the production of the convulsions, since Sarbo<sup>12</sup> called the attention to the high percentage of persons with lead poisoning (printers) in a group of patients with tetany that he studied.

The combination of *parathyroid insufficiency with a central lesion* that lowers the convulsive reactivity is, of course, rather rare. The following case observed by the author and reported in more detail elsewhere<sup>13</sup> may demonstrate, however, that such a combination is not a mere theoretical construction and may shed some light upon the part played by the central factor in the pathogenesis of tetany spasms.

CASE I.—In a twenty-three-year-old nurse a left-sided hemiparesis developed following strumectomy. In the paretic left arm, attacks of painful spasms appeared with consciousness unimpaired. In these attacks the left hand assumed the typical "obstetric position." The Trousseau sign could be elicited in the left arm only. There was a slight Chvostek sign on both sides, which was somewhat stronger on the left than on the right. After implantation of parathyroids into the abdominal skin this overexcitability decreased.

In this instance a softening in the right internal capsule apparently developed following the strumectomy, probably as a result of an embolus. It was assumed that the operation

In the group of attacks of functional origin that may imitate tetany, one should also include the *breath-holding spells* that appear in nervous children following emotional excitement. The close relationship of these spells to an emotional upset, and their sudden termination and their response to psychotherapeutic measures will help to differentiate them from true laryngospasm. It may sometimes be more difficult to recognize the true nature of the *laryngospasm* caused by *intracranial hemorrhage* following birth trauma, particularly since it may be associated in these infants with a positive Chvostek sign. The examination of the blood calcium will be an important differential diagnostic aid.

*Carpopedal spasms* may also be caused by conditions other than tetany (e.g., by strong reflex stimuli). I had occasion, some years ago, to watch a thirty-five-year-old neurotic during the perforation of his appendix into the peritoneal cavity, a perforation which was later confirmed at operation. During the attack of pain suffered by the patient in the moment of perforation a typical spasm with "obstetric position" of both hands appeared. Guild<sup>10</sup> mentions that children on the verge of or just recovering from a convulsion due to any cause often show the feet stiffly extended and the toes flexed as in the pedal spasms of tetany, and that also positions of the hands suggestive of carpal spasms may be observed although there is rarely the sharp flexion at the wrist seen in true carpal spasms. It will not be difficult to differentiate such pseudocarpal or pedal spasms from those of tetany, if one considers the conditions under which they appear as well as allied symptoms.

In some instances, particularly in young infants, the *clonic component of the convulsions* predominates. As a rule, consciousness is not impaired in convulsions due to tetany; it is also rather easy to differentiate convulsions that are associated with mental defects and/or various disturbances of motility (paresis, athetosis) and sensation, such as convulsions due to malformations, birth injuries, degenerative diseases of the brain, or those associated with fever or changes in the spinal fluid, as in meningitis or encephalitis. Occasionally, however, convulsions of tetany may be precipitated by *infectious dis-*

Barre,<sup>20</sup> the head of a dog was connected only by way of the vagi with the rest of the body and was perfused with the blood of another dog. Hypoglycemia of the cephalic blood inhibited, hyperglycemia increased the output of insulin through vagal impulses.\*

For an evaluation of the neurogenic factor in diabetes mellitus, it is of importance to ascertain whether central lesions are able to produce permanent glycosurias. As a rule, the effect of the puncture of the floor of the fourth or the third ventricle is only transitory, and only occasionally glycosurias of several weeks' duration were observed following hypothalamic lesions (Camus, Gourray, and Le Grand;<sup>21</sup> Strieck<sup>22</sup>). Thus the present experimental material seems insufficient to support the assumption of a purely centrogenic origin of diabetes mellitus. The results of histopathologic studies point in a similar direction, although more or less transient glycosurias were observed in tumors of the floor of the fourth ventricle, in hemorrhages, softenings, tumors of the hypothalamus (Lhermitte, MacCollom) and lesions of the caudate nucleus (Lépine).

For our problem the histopathological findings in typical cases of diabetes mellitus are more important. Degenerative changes in the nuclei around the floor of the third ventricle were reported by various authors (Leschke, Marinesco and Paulian, Inaba), and exact cell counts of hypothalamic nuclei (Morgan, Malone and Vonderahe<sup>23</sup>) gave a definite proof of cell loss. As I have pointed out elsewhere,<sup>24</sup> one has to bear in mind that one deals here with brains of patients who suffered from chronic metabolic disorders, and that many of these patients died in diabetic coma. A careful study of the brains of these patients reveals not only changes in the vegetative centers, but also in other nuclei. Therefore, the conclusion

\* It is still uncertain whether the hypothalamus also influences the production of the diabetogenic hormone of the anterior pituitary. The experience that hypothalamic lesions attenuate pancreatic diabetes (Davis, Cleveland and Ingram,<sup>17</sup> Cleveland and Davis<sup>18</sup>) in the same manner as hypophysectomy attenuates the diabetes (Houssay<sup>19</sup>) of pancreatectomized animals, may perhaps be interpreted in such a way. It is difficult, however, to draw definite conclusions from these experiments, since sections of the pituitary stalk do not have a similar effect.

had also injured the parathyroids but that this injury was not sufficient to produce manifest symptoms of tetany, otherwise spasms would have appeared also in the right side of the patient. The loss of impulses from the right cortex had induced a state of overexcitability in the respective subcortical centers, so that they reacted to the metabolic changes associated with impairment of the parathyroids, and spasms developed in the respective half of the body.

In order to test this theory, Spiegel and Nishikawa<sup>14</sup> combined partial parathyroidectomies in dogs with hemisection of the midbrain. They observed that only those extremities in which the lesions of the midbrain had produced the picture of decerebrate rigidity showed spontaneous spasms or an increased tendency toward spasm. These observations seemed to indicate that *central lesions* increasing the excitability of those subcortical ganglia upon which the innervation of tetany spasms depends *may facilitate the development of such spasms*, if the activity of the parathyroids is impaired.

#### HYPERGLYCEMIA-DIABETES MELLITUS

If one studies autopsies in cases of diabetes mellitus, one is often astonished how slightly the islands of Langerhans are affected. Such experiences point to the possible importance of the neurogenic factor in this disease. Clinically it is well known that psychic trauma may precipitate the outbreak of true diabetes or may induce an increase of its manifestations. The mechanism of such effects is indicated by the experimental analysis of Claude Bernard's piqure (puncture of the floor of the fourth ventricle) which sets forth impulses carried by the splanchnics to the adrenals and to the liver. Thus glycogenolysis is accelerated in the latter gland partly by direct action of the splanchnics, partly indirectly by increased output of adrenalin. This latter factor is probably also chiefly responsible for the hyperglycemia and glycosuria caused by hypothalamic lesions, since stimulation of the hypothalamus also induces a liberation of adrenalin (Houssay and Molinelli,<sup>15</sup> Karplus and Kreidl<sup>16</sup>).

Inhibition of the pancreas by way of the vagi may also play a part. In the interesting experiments of Zuntz and La

Barre,<sup>20</sup> the head of a dog was connected only by way of the vagi with the rest of the body and was perfused with the blood of another dog. Hypoglycemia of the cephalic blood inhibited, hyperglycemia increased the output of insulin through vagal impulses.\*

For an evaluation of the neurogenic factor in diabetes mellitus, it is of importance to ascertain whether central lesions are able to produce permanent glycosurias. As a rule, the effect of the puncture of the floor of the fourth or the third ventricle is only transitory, and only occasionally glycosurias of several weeks' duration were observed following hypothalamic lesions (Camus, Gourray, and Le Grand;<sup>21</sup> Strieck<sup>22</sup>). Thus the present experimental material seems insufficient to support the assumption of a purely centrogenic origin of diabetes mellitus. The results of histopathologic studies point in a similar direction, although more or less transient glycosurias were observed in tumors of the floor of the fourth ventricle, in hemorrhages, softenings, tumors of the hypothalamus (Lhermitte, MacCollom) and lesions of the caudate nucleus (Lépine).

For our problem the histopathological findings in typical cases of diabetes mellitus are more important. Degenerative changes in the nuclei around the floor of the third ventricle were reported by various authors (Leschke, Marinesco and Paulian, Inaba), and exact cell counts of hypothalamic nuclei (Morgan, Malone and Vonderahe<sup>23</sup>) gave a definite proof of cell loss. As I have pointed out elsewhere,<sup>24</sup> one has to bear in mind that one deals here with brains of patients who suffered from chronic metabolic disorders, and that many of these patients died in diabetic coma. A careful study of the brains of these patients reveals not only changes in the vegetative centers, but also in other nuclei. Therefore, the conclusion

\* It is still uncertain whether the hypothalamus also influences the production of the diabetogenic hormone of the anterior pituitary. The experience that hypothalamic lesions attenuate pancreatic diabetes (Davis, Cleveland and Ingram;<sup>17</sup> Cleveland and Davis<sup>18</sup>) in the same manner as hypophysectomy attenuates the diabetes (Houssay<sup>19</sup>) of pancreatectomized animals, may perhaps be interpreted in such a way. It is difficult, however, to draw definite conclusions from these experiments, since sections of the pituitary stalk do not have a similar effect.



had also injured the parathyroids but that this injury was not sufficient to produce manifest symptoms of tetany, otherwise spasms would have appeared also in the right side of the patient. The loss of impulses from the right cortex had induced a state of overexcitability in the respective subcortical centers, so that they reacted to the metabolic changes associated with impairment of the parathyroids, and spasms developed in the respective half of the body.

In order to test this theory, Spiegel and Nishikawa<sup>14</sup> combined partial parathyroidectomies in dogs with hemisection of the midbrain. They observed that only those extremities in which the lesions of the midbrain had produced the picture of decerebrate rigidity showed spontaneous spasms or an increased tendency toward spasm. These observations seemed to indicate that *central lesions* increasing the excitability of those subcortical ganglia upon which the innervation of tetany spasms depends *may facilitate the development of such spasms*, if the activity of the parathyroids is impaired.

#### HYPERGLYCEMIA—DIABETES MELLITUS

If one studies autopsies in cases of diabetes mellitus, one is often astonished how *slightly* the islands of Langerhans are affected. Such experiences point to the possible importance of the neurogenic factor in this disease. Clinically it is well known that psychic trauma may precipitate the outbreak of true diabetes or may induce an increase of its manifestations. The mechanism of such effects is indicated by the experimental analysis of Claude Bernard's *piqûre* (puncture of the floor of the fourth ventricle) which sets forth impulses carried by the splanchnics to the adrenals and to the liver. Thus glycogenolysis is accelerated in the latter gland partly by direct action of the splanchnics, partly indirectly by increased output of adrenalin. This latter factor is probably also chiefly responsible for the hyperglycemia and glycosuria caused by hypothalamic lesions, since stimulation of the hypothalamus also induces a liberation of adrenalin (Houssay and Mollinelli,<sup>15</sup> Karplus and Kreidl<sup>16</sup>).

Inhibition of the pancreas by way of the vagi may also play a part. In the interesting experiments of Zuntz and La

*potrichosis* following encephalitis (Kennedy<sup>29</sup>) may also be mentioned in this connection, although it is uncertain whether it was due to stimulation of the adrenals or of the gonads.

Signs and symptoms of hypofunction or *insufficiency* of the adrenal cortex may also appear unaccompanied by demonstrable anatomical changes of this gland (Addison,<sup>30</sup> Laignel-Lavastine,<sup>31</sup> Pende and Varvaro,<sup>32</sup> Spiegel and Adolf<sup>3</sup>). Thus the question whether hypofunction of the adrenal cortex might be caused by a primary lesion of the sympathetic system confronted even early investigators. The following observation reported by Dr. Adolf and myself may illustrate the problems presented by this type of cases.

CASE II.—In a seventy-five-year-old lady a syndrome of asthenia, gastrointestinal disturbances, anorexia, occasional vomiting, constipation, and pigmentation on the hands, in the axillary skin, in the buccal mucous membrane and in the palate, developed. The temperature was subnormal. Besides meteorism, there was some free fluid in the abdomen and edema in the lower extremities. The systolic blood pressure was 155. There was no sign of diabetes or leukemia, and also no indication of a skin disease or an intoxication that could explain the pigmentation.

At *autopsy* no signs of a tuberculosis or of a carcinoma could be found. The endocrine glands and liver were without pathological changes. A diagnosis of atypical Addison's disease was made. (Neusser reported Addison's disease in an eighty-year-old man, and Birtorf a case with a blood pressure of 155.) *Histologically* both adrenals were intact. The solar plexus and the upper cervical ganglion showed severe pigmentation of all the cells; even the small cells, that remain unpigmented in the aged, were filled with lipoid pigment. In some cells there was formation of vacuoles, occasionally also neuronophagia. The interstitial tissue showed slight round cell infiltration.

An evaluation of these findings is rather difficult, since we observed similar changes, although somewhat slighter (atrophy and pigmentation of the cells of the sympathetic ganglia), as secondary effects caused by necrosis of the adrenals. Thus the histopathological findings do not permit one to decide how far the changes in the sympathetic nervous system are the cause and how far they are the effect of adrenal insufficiency.

Observations of cases in which fatal insufficiency and atrophy of the adrenals developed following denervation of the gland, as in the cases reported by Rogoff,<sup>33</sup> and by Snell, Wilder and Cragg,<sup>34</sup> are, therefore, of importance. The

seems warranted that most of the cellular changes found in the hypothalamic nuclei of diabetics are the consequence, and not the cause, of the metabolic disorder. Thus, there is no proof that a purely centrogenic form of diabetes exists. This does not exclude, of course, the possibility that impulses originating in the vegetative centers may determine the severity and accelerate the fatal course of the disease. Such impulses may be caused partly by psychic or reflex stimuli. It seems not impossible that also the degenerative changes produced by diabetic acidosis in the hypothalamic nuclei could increase the intensity of the metabolic disorder, so that a vicious circle becomes eventually established.

This influence of the central factor upon the severity of the diabetes is well illustrated by a case of thalamic cyst reported by Niemer and Vonderahe.<sup>25</sup> The cyst obstructed the anterior orifice of the aqueduct of Sylvius and caused the development of an internal hydrocephalus. The clinical signs and symptoms included a typical diabetes mellitus which varied in intensity, apparently with the degree of the hydrocephalic pressure on diencephalic structures.

#### ADRENAL SYMPTOMS

It has already been pointed out, in the discussion of hyperglycemias of central origin, that impulses from the higher vegetative centers reaching the adrenal medulla by way of the splanchnics may increase the liberation of epinephrine into the circulation. It is not as certain, however, that the adrenal cortex may also be influenced by the central nervous system. It appears from the studies of MacFarland and Davenport<sup>26</sup> that anatomically the nerve fibers entering the adrenals pass through the outer layers of the gland making functional connections with the medulla only, while no evidence of innervation of the adrenal cortex could be found by these authors. Cases of hyperfunction of the adrenal cortex without morphological changes in this organ (Broster<sup>27</sup>) and in the pituitary (de Jongh<sup>28</sup>) suggest the possibility that hypothalamic impulses may influence the production of the adrenotropic hormone of the anterior pituitary. This problem, however, needs experimental analysis. The occurrence of hy-

centers in the vicinity of the third ventricle. This was demonstrated for the hypothalamic vasomotor centers by Spiegel and Saito<sup>39</sup> (1924), who found by this route a vasodilator action of small, intravenously ineffective amounts of pituitrin. (Rediscovered by Cushing<sup>40</sup> in 1931.) For the effect of pituitrin upon the water exchange Pick<sup>41</sup> and his school have tried to demonstrate a central action of this hormone. Although experiments of Starling and Verney<sup>42</sup> indicate that the chief site of the antidiuretic action of pituitrin lies in the kidney, Pick's work suggests that this hormone may also influence a diencephalic mechanism concerned with the water metabolism of the body; thus in the pituitrin-refractory cases of diabetes insipidus one could deal with lesions affecting the central site of action of pituitrin.

Furthermore, in some of the pituitrin-refractory cases one may note that the thirst of the patients is particularly unresponsive to the hormone. While in the diabetes insipidus produced experimentally in cats and rats by lesion of the supraoptico-pituitary system, the polyuria is considered the primary disturbance\* (Ranson,<sup>35</sup> Richter<sup>43</sup>), this clinical experience seems to indicate that there exists a form of diabetes insipidus in which thirst is the primary factor. Such a view is corroborated by experiments of Bellows and Van Wageningen<sup>44</sup> on dogs in which the polydipsia and the polyuria were separated by establishing esophageal fistulas. These authorities found that the permanent phase of the diabetes insipidus, that they produced by hypothalamic injuries, resolved itself into polydipsia. Summing up, it seems that *two pathogenetically different groups of diabetes insipidus* should be differentiated: one caused by deficiency of the antidiuretic hormone (due to lesion of the posterior lobe or of the supraoptico-pituitary system) and a second formed by pituitrin-refractory cases in which the diencephalic lesion either affects a central site of action of pituitrin or produces a primary polydipsia.

#### GENITAL DYSFUNCTION

That emotions may influence the potency in the male as well as menstruation in the female is commonly noted. In

\* In these experiments the polyuria preceded the polydipsia.

changes reported were, however, at least partly due to unavoidable operative interference with the blood supply of the glands.

Recently Bauer and Aschner<sup>35</sup> expressed the interesting view that the "formes frustes" of Addison's disease might be due to vegetative disturbances. These atypical forms are found in individuals with a labile vegetative nervous system and are manifested by asthenia, fatigue, slight vascular hypotension, gastro-intestinal symptoms, slight pigmentation. The benign nature of the disease makes it, of course, impossible to prove or disprove Bauer's thesis, as long as some accidental autopsy findings are not available.

#### DIABETES INSIPIDUS

Deficiency of the antidiuretic principle of the posterior pituitary, inducing diabetes insipidus, may be caused either by destruction of this lobe or by elimination of the impulses which it receives from the hypothalamus (bilateral destruction of the nucleus supraopticus, section of the stalk of the pituitary, Fisher, Ingram and Ranson<sup>35a</sup>). It would, however, be an oversimplification, if one would follow the trend of many recent authors who try to explain diabetes insipidus as due merely to the lack of secretion of the posterior lobe. Such a conception holds for a group of cases in which the replacement of the insufficiently produced antidiuretic principle is able to reduce the fluid exchange to more or less normal level.

One has, however, to bear in mind that there is a group of cases of diabetes insipidus which are refractory to pituitrin, as shown by experiences in diencephalic lesions due to encephalitis (Hoff and Wermer,<sup>36</sup> Snell and Rowntree<sup>37</sup>) or to extensive tumors (Biggart<sup>38</sup>). Thus the question arises whether or not some forms of diabetes insipidus may be caused by other mechanisms than by injury to the posterior pituitary or to the supraoptic-hypophyseal tract.

There exists a mutual relationship between the posterior lobe and the hypothalamus not only in the sense that the former receives nervous impulses from hypothalamic nuclei, but also conversely in that its secretion acts upon vegetative

praecox was caused by pathologic changes in the diencephalon (Luce,<sup>50</sup> Schaechter<sup>51</sup> and Grant and Weinberger<sup>52</sup>), while the endocrines, including pineal gland and pituitary, were apparently morphologically normal. An interpretation of these cases seems, at present, rather hazardous. It is certainly not warranted to draw the conclusion, as some authors do, that in all cases of pineal tumors this syndrome is due to pressure upon the diencephalon. The existence of vegetative centers in this region, inhibiting the sexual development, is not yet proved by any experimental evidence, and one must admit that the appearance of this symptom in diencephalic lesions may just as well be due to functional impairment of the adjoining glands, since the present histological methods are not always able to detect a morphologic equivalent of such an impairment. The only safe conclusion one can draw is that the diagnostic consideration in a case of *pubertas praecox* should include tumor of the pineal gland as well as diencephalic disease.

#### GALACTORRHEA

There are a few cases on record in which galactorrhea was apparently caused by hypothalamic lesions (encephalitis, tumor leaving the pituitary intact, Scheer and Hemmes<sup>53</sup>). One may assume that these lesions produced an increased liberation of the lactogenic hormone of the anterior pituitary.

#### OBESITY

It was first recognized by Erdheim<sup>54</sup> that the adiposity observed in some patients with tumors of the pituitary may be caused by lesions of the base of the brain. Erdheim's conclusions were corroborated by experimental studies (Camus and Roussy,<sup>55</sup> Bailey and Bremer,<sup>56</sup> Smith,<sup>57</sup> and Ranson and Hetherington<sup>58</sup>). The experiments (particularly those of Smith<sup>57</sup>) showed that extensive bilateral tuberal lesions, leaving the pituitary gland intact, were able to produce obesity, while total extirpation of this gland failed to have such an effect, if the hypothalamus was not injured. Clinical and pathological observations (Cushing<sup>59</sup>) are in agreement with this

hypothalamic lesions amenorrhea in the female, loss of potency and diminution of libido in the male, and eventually regressive changes of the sex organs, may develop, usually associated with cerebral adiposity (to be described later), as has been repeatedly observed in recent decades, particularly in cases of epidemic encephalitis. Occasionally such disturbances are produced by hypothalamic lesions without the development of obesity (Brooks<sup>45</sup>). These disorders seem to be due chiefly to interference with the influence of the hypothalamus upon the release of gonadotropic hormones by the anterior pituitary. The existence of such an influence is indicated by the experience that electric stimulation of the hypothalamus is able to elicit ovulation (Marshall and Verney<sup>46</sup>), and that section of the pituitary stalk prevents, not only such an effect of electric stimulation of the hypothalamus (Westman and Jacobsohn<sup>47</sup>), but also the ovulation occurring following coitus in rabbits (Brooks<sup>45</sup>).

#### PUBERTAS PRAECOX

In the presence of the syndrome of precocious sexual maturity the differential diagnosis necessitates consideration of diseases of the genital glands or adrenals as well as of the pineal gland, pituitary body and of diencephalic vegetative centers. A discussion of the controversial question, whether the pineal gland normally inhibits the sexual development (Marburg<sup>49</sup>) or not, is beyond the scope of this paper. As for the question of local diagnosis, there seems to exist ample evidence that pineal tumors in children (particularly boys—Marburg), completely destroying this gland, are often associated with premature sexual development; thus the presence of this syndrome makes it imperative to search for signs of increased intracranial pressure and of compression of the midbrain and diencephalon in particular (compression of the aqueduct, enlargement of the third and of the lateral ventricles, compression of the oculomotor nuclei, development of Nothnagel's syndrome of bilateral, incomplete third nerve paralysis associated with cerebellar ataxia).

There are, however, also cases on record in which pubertas

how far these possibilities play a part in the genesis of obesity in tuberal lesions.

#### SIMMONDS' CACHEXIA AND ANOREXIA NERVOSA

While it is relatively easy, as a rule, to recognize the usual causes of emaciation such as tuberculosis, malignant diseases, hyperthyrotoxicosis, the differential diagnosis between Simmonds' cachexia and anorexia nervosa may cause difficulties, both conditions having cardinal features in common such as loss of weight, genital dysfunction (loss of libido, amenorrhea and impotence respectively), and low basal metabolism. Development of these symptoms following a pregnancy, x-ray findings of calcifications, or other anomalies in the sella turcica speak in favor of Simmonds' cachexia. In a recent review Escamilla and Lissner<sup>67</sup> are inclined to regard loss of axillary and pubic hair also as indicative of Simmonds' disease; this latter sign seems, however, a less reliable criterion. Depressive mood, nearly unsurmountable anorexia, absence of pregnancies in the history of the female patient, development of the disease following psychic trauma, favorable effect of therapeutic procedures, particularly of psychotherapy, make the diagnosis of anorexia nervosa probable.

The difficulties of the differential diagnosis between these two conditions suggest a pathogenetic relationship in that Simmonds' cachexia is due to organic lesions of the anterior lobe of the pituitary, while anorexia may be caused by functional inhibition of this gland. Bauer and Aschner<sup>35</sup> assume that inhibition of long duration may eventually lead to atrophy of the specific cells; this interesting theory must, however, remain hypothetical as long as autopsy findings of atrophy of the anterior lobe are not reported in cases in which causes other than nervous inhibition are definitely excluded.

It is also difficult to evaluate the pathogenetic role of the nervous factor in such cases as those described by Gallavan and Steegmann<sup>68</sup> in which atrophy of the anterior lobe was associated with degenerative changes in the hypothalamus. Because of the close proximity of the pituitary and of the tuber, the lesions of these two structures may be caused by a



conception. Obesity was, for instance, observed in suprasellar tumor or in cases of epidemic encephalitis (Economo,<sup>60</sup> Lhermitte<sup>61</sup>) in which the pituitary gland was histologically intact.

One has, of course, to bear in mind that obesity caused by cerebral dysfunction or disease is rather rare, and that such a diagnosis should be made clinically only if there are other indications of an involvement of the brain and extracerebral causes can be excluded, since the type of fat distribution alone does not allow one to draw definite pathogenetic conclusions. Lhermitte<sup>61</sup> tried to differentiate obesity of hypothalamic origin from the pituitary type in that the first shows Fröhlich's "girdle type" of obesity (chief localization: hips, mons veneris, thighs, buttocks), while the latter is represented by the obesity seen in Cushing's syndrome (face, neck and trunk affected). The validity of such a differentiation is, however, questionable (Riddoch,<sup>62</sup> and Gildea and Man<sup>63</sup>), and the diagnosis of cerebral obesity still depends upon the existence of allied cerebral symptoms (e.g., increased intracranial pressure, thalamic syndromes, sleepiness, hypothermia).

It is still uncertain through which mechanism obesity develops in tuberal lesions. Several possibilities should be considered. On the one hand the lesion may affect impulses descending toward the spinal cord which influence the storage of fat in the liver (Raab<sup>64</sup>) or in the subcutaneous fat tissue directly (Hausberger<sup>65</sup>). On the other hand, a hypothalamic lesion may interfere with functions of the pituitary that are related to the fat metabolism of the body. The experience that total hypophysectomy does not induce obesity does not preclude an influence of this gland upon the fat metabolism. In fact, it seems that incomplete lesions of the pituitary are more effective in producing disturbances of the fat metabolism than total hypophysectomies (Keller, Noble and Hamilton<sup>66</sup>), similarly as it is known from experimental diabetes insipidus. Thus it is not improbable that interference with the output of gonadotropic hormone may produce a syndrome, similar to Fröhlich's syndrome, by impairing the function of the gonads, or that increase of the output of adrenotropic hormone may evoke a type of obesity similar to that observed in Cushing's syndrome. Further studies will have to ascertain

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common pathologic process. In any case the possibility should be admitted that emaciation may result from hypothalamic lesions. Cases of tumors have been recorded that produced emaciation following an initial stage of obesity (Cushing<sup>40</sup>), but these cases hardly give an answer to the question of whether or not lesions of certain parts of the hypothalamus may lead to cachexia. Some observations (Bailey and Bremer<sup>46</sup>) in tubercular lesions indicate such a possibility; however, further experimental work regarding this problem seems necessary.

### PSEUDO-ACROMEGALY

Cheiriomegaly (enlargement of the hands) as well as podomegaly (enlargement of the feet) may be observed in cases of syringomyelia apparently due to "trophic" disturbances caused by involvement of the segmental vegetative centers in the spinal cord. As a rule it is not difficult to differentiate this condition from true acromegaly. There will be in syringomyelia disturbance of pain and temperature sensation associated with development of ulcers in the affected parts; the enlargement will not be strictly symmetrical as in acromegaly (owing to asymmetrical involvement of the cord) and it will not be limited to the acra, but involve the hand or foot as a whole, as may be demonstrated, if necessary, by x-ray examination. As was pointed out by Kroll,<sup>49</sup> it is doubtful whether or not acromegalic signs may appear as sequelae of encephalitis.

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## THE DIAGNOSTIC VALUE OF HORMONE ASSAYS\*

A. E. RAKOFF, M.D.†

MUCH of the progress which has been made in clinical endocrinology during the last decade has resulted from the demonstration of various hormones in the body fluids and the correlation of these findings with the clinical picture. The information thus acquired has served not only in affording a better understanding of normal and disturbed endocrine physiology but has also helped in establishing an etiological basis for various endocrine dysfunctions and has suggested better methods of therapy. All this has occurred despite the fact that most of the tests for hormone assays are difficult, expensive, time-consuming, and require extensive laboratory facilities. Even then the results often cannot be interpreted except in the light of the clinical findings. These objections, however, do not minimize the fact that where such studies are available they frequently yield information which cannot be obtained in any other way.

The majority of these tests are done by biologic assay methods and are subject, therefore, to the difficulties inherent in such procedures. Recently, however, chemical methods have been described for some of the hormones and in some instances these have replaced the biologic assays.

### GONADOTROPIC HORMONES

The gonadotropic principle of the anterior pituitary behaves as though it consists of two distinct hormones, although there is some disagreement as to whether they are actually distinct entities. The first of these gonadotropins is now

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commonly referred to as the follicle-stimulating hormone (F.S.H.) formerly commonly known as prolan A; while the second fraction is called the luteinizing hormone (L.H.) corresponding to the older term prolan B. The follicle-stimulating fraction is gametokinetic, stimulating the growth of ova and thecal cells in the ovary and spermatogenesis in the testis, while the luteinizing fraction appears to stimulate the interstitial cells (therefore also referred to as I.C.S.H., interstitial-cell-stimulating hormone) resulting in luteinization in the female and stimulation of the interstitial cells of Leydig in the male.

Another distinct gonadotropin appears in very large amounts in the blood and urine during pregnancy. It is generally agreed that this hormone is secreted by the chorionic tissue of the placenta and is therefore referred to as "chorionic gonadotropin." The effect of this hormone is primarily on the interstitial cells yet it differs in many ways from the luteinizing hormone of the hypophysis; therefore, the designation of "anterior pituitary-like" hormone (A.P.L.) is no longer apropos.

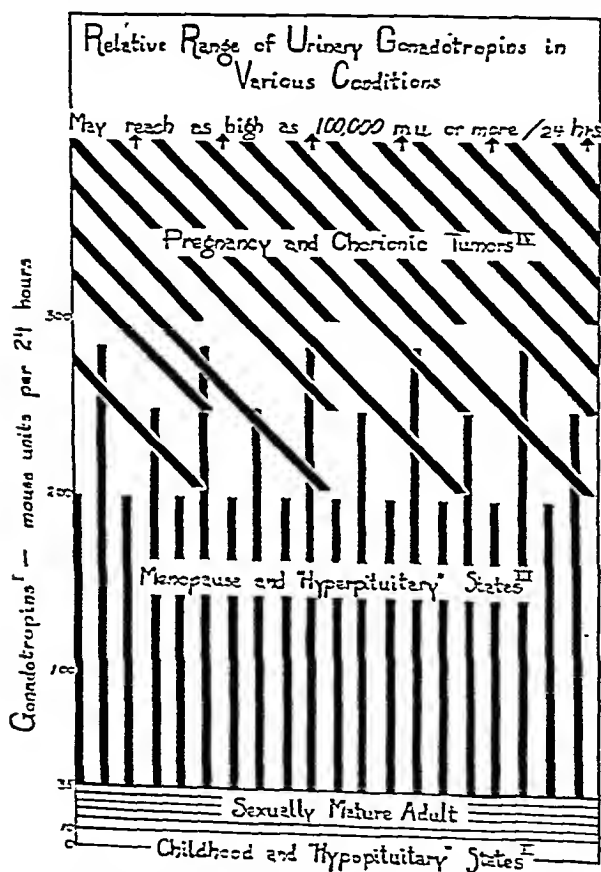
### Methods of Assay

The most commonly employed methods for assaying gonadotropins are based upon the injection of serum or urine or their purified extracts into immature rodents. The hormone in the urine is generally precipitated with alcohol or tannic acid and purified. Many biologic end-points for the determination have been employed including (a) increase in weight of the seminal vesicles, (b) vaginal estrus, (c) increase in weight of the ovaries, (d) increase in weight of the uteri and (e) production of corpora lutea. The choice of method depends mainly upon the type of gonadotropins present; when this is unknown or when a mixture of gonadotropins are present, as is frequently the case, a combination of methods may be employed.

In normal individuals the amount of gonadotropins present in blood and urine varies tremendously in different physiologic states (Fig 235). Thus in childhood the amount of hormone may be too small to detect, whereas in pregnancy as much as 100,000 mouse units or more of chorionic gonadotropin may be excreted in twenty-four hours. The type of gonadotropin present also varies, in the sexually mature period a mixture of the follicle-stimulating and luteinizing factors is present, in the climacteric the hormone is chiefly of the follicle-stimulating type, while during pregnancy only the chorionic gonadotropin is present. The method of assay employed and its sensitivity must therefore be selected on the basis of the clinical status.

## Normal Gonadotropin Values

*Childhood.*—It is usually not possible to detect the presence of gonadotropins in the blood or urine before about the age



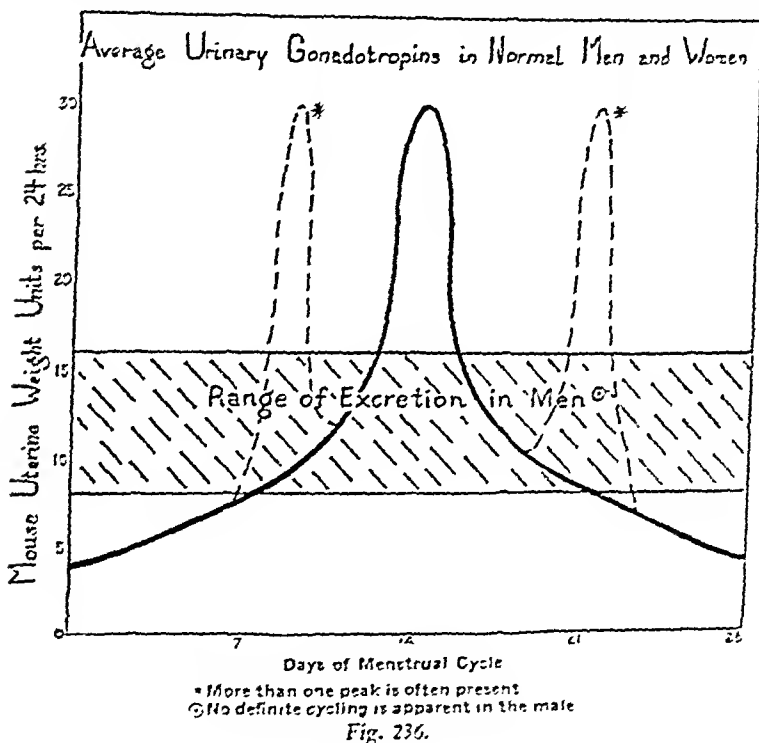
- I. Unit varies with type of gonadotropin present.
- II. May be absent or only traces present.
- III. Chiefly follicle-stimulating hormone.
- IV. Chorionic gonadotropin.

Fig. 235.

of eleven years. In girls it is often possible to detect small amounts of follicle-stimulating hormone as early as a year before the onset of the first menstruation, while in boys a

positive response cannot usually be obtained before the age of twelve or thirteen years.<sup>1, 2, 3</sup>

*Reproductive Period.*—Male.—Small amounts of gonadotropic hormone may be regularly demonstrated in urine extracts of the sexually mature male. The hormone appears to be chiefly or entirely of the follicle-stimulating type.<sup>4</sup> Considerable daily variation in the gonadotropin excretion has



been noted, but no definite cyclic periodicity is present as in the female.<sup>5</sup> In our laboratory the gonadotropic values in normal males average about 8 mouse uterine-weight units per twenty-four hours with a range varying from traces to 16 mouse uterine-weight units per twenty-four hours.

The amount of gonadotropic hormone in the blood is usually too small to be demonstrated by the ordinary methods for clinical assays.

**Female.**—Varying amounts of gonadotropic hormone may be demonstrated in urine extracts throughout most of the menstrual cycle in normal adult females. During the first week of the cycle the amount of hormone is usually quite low (ranging from traces to 8 mouse uterine-weight units). As the midcycle is approached the titer suddenly rises and may reach a peak of 30 mouse uterine-weight units or more, and then suddenly drops (Fig. 236). It is now well established that more than one such peak may appear during some cycles; it is not known whether this indicates that more than one ovulation has occurred. Since such increases in excretion may occur quite suddenly it is necessary to make assays at frequent intervals if this is to be used as evidence of normal pituitary stimulation for ovulation.

Evidence of gonadotropic hormone in the blood or serum may usually be demonstrated at the midcycle or during peaks in gonadotropin excretion.<sup>6</sup>

**Climacteric.**—It is well known that the majority of menopausal women excrete increased amounts of gonadotropic hormone. The increased gonadotropin titers may appear several years before any alteration in the menses is evident and may persist for many years after its cessation. The urinary hormone values are generally consistently higher than the normal "ovulatory" peak and occasionally even enough hormone may be present to give a "false" positive pregnancy test. The range is usually from 30 to 200 or more mouse uterine-weight units each twenty-four hours. Sufficient hormone is also present in the blood to produce a marked ovarian response in infantile animals after the injection of 4.5 cc. of serum or less. Similar findings quite regularly occur after castration or in primary hypogonadism of other origin.

Occasionally increased gonadotropin excretion occurs in men past fifty; the finding however is rare as compared to menopausal women. Very often, however, high levels of gonadotropins comparable to those of menopausal women occur in men who have been castrated or who have other evidences of primary testicular insufficiency.<sup>7</sup>

## Pregnancy and Pregnancy Tests

As early as ten days after conception an increase in gonadotropins may be detected in the blood and urine and within a week after the first missed period a sufficient concentration of the hormone is present in the urine to give a positive "pregnancy" test. This hormone is a chorionic gonadotropin (or "anterior-pituitary-like" hormone) and is secreted by the chorionic tissue of the placenta. It is almost entirely a lutein-

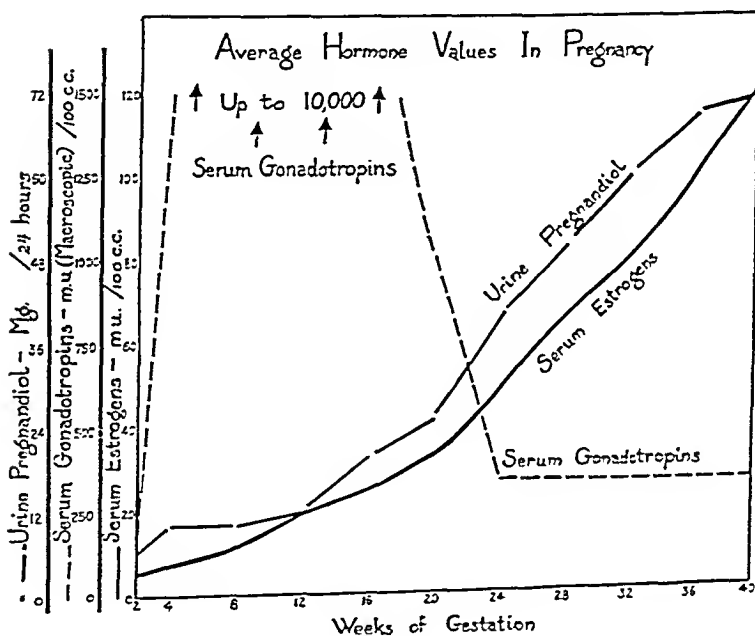


Fig. 237.

izing hormone but differs in many respects from the gonadotropins of nonpregnant women. Its concentration rises rapidly to reach very high values between the sixth and sixteenth weeks of gestation (Fig. 237). During this period average values commonly reach as high as 10,000 mouse uterine-weight units per 100 cc. of blood and a transient peak up to 30,000 may be detected. In the urine the twenty-four-hour values are about ten times as much. After the twentieth week

the hormone level falls and during the last half of gestation the values remain quite constant at from 300 to 500 mouse uterine-weight units per 100 cc. of serum.

Following the delivery of the placenta the gonadotropins fall rapidly and within a week they have generally reached nonpregnant levels, although occasionally titers sufficient to give a positive pregnancy test may persist for several weeks, particularly if placental fragments have been retained.

The demonstration of increased amounts of gonadotropic hormone in the urine or blood is the basis for the reliable tests for pregnancy. The two technics which have stood the test of time are the Friedman and the Aschheim-Zondek tests. Properly done, both of these tests are highly reliable and unquestionably constitute the most generally useful of the clinical hormone studies. The frog (*Xenopus*) also appears to be a reliable test animal and has the advantage of rapidity, making it useful in the diagnosis of such emergencies as ectopic pregnancy.<sup>8</sup> Frank and Berman have recently reported on a modification of the Aschheim-Zondek test in which a reading may be obtained as early as six hours.<sup>9</sup>

#### Gonadotropin Assays for Clinical Diagnosis

*Menstrual and Related Disturbances.*—The determination of urinary gonadotropins at frequent intervals may aid in establishing the nature of certain menstrual disturbances. Thus, in nonpregnant women with amenorrhea or hypomenorrhea due to primary ovarian failure, high levels of gonadotropins are quite regularly encountered. This may occur in young girls<sup>10</sup> as well as in normal menopausal women or surgical castrates. In other young amenorrheic women repeated assays may fail to demonstrate any appreciable excretion of gonadotropins. This may occur not only in those rare instances of advanced hypophyseal failure (Simmonds' disease) and true cases of Fröhlich's disease but also quite commonly in obese women who are otherwise normal.

In hypermenorrhea of functional origin the gonadotropin excretion may be normal, high or diminished. The result should be correlated with the estrogen and pregnandiol excretion as well as with endometrial biopsies in order to de-

termine whether the disturbance is primarily pituitary or ovarian in origin. Unless a consistently high excretion is noted the assays should be repeated at weekly intervals through a cycle.

Many cases of functional sterility in the female appear to be due to insufficient gonadotropic stimulation to produce normal ovulation. This diagnosis would be favored by the failure to find a peak of gonadotropin excretion on frequently repeated examinations, especially in conjunction with confirmatory evidence by endometrial biopsy.

*Testicular Abnormalities.*—The excellent results with chorionic gonadotropin in the treatment of many cases of cryptorchidism suggests that the failure of the testicles to descend, particularly by the age of twelve or thirteen years, may be due to a lack of normal gonadotropic stimulation. In young children this is difficult to ascertain because of the normally very low or absent urinary gonadotropin excretion; on the other hand we have been unable to demonstrate gonadotropin in a number of such boys even beyond the age of eleven, who later responded to chorionic gonadotropin. In such instances there is also a diminution in androgen and 17-ketosteroid values.

As in the female some instances of testicular deficiency and sterility may be the result of diminished pituitary function. These do not appear to be as common in the male as in the female. In this group also fall true cases of Fröhlich's syndrome.

It has already been indicated that in primary testicular deficiencies, whether of organic or functional origin, a secondary rise in gonadotropins usually occurs. Gonadotropin assays may be useful in distinguishing ordinary fat boys from those who are suspected of having the latter condition.

*Tumors of Chorionic Origin.*—*Testicular Tumors.*—It is well known that chorionepithelioma of the testis produces large amounts of gonadotropic hormone. Generally these are sufficiently high to give a positive Friedman or Aschheim-Zondek test. Because of the rapidly progressive and highly fatal nature of this disease, in all suspicious cases quantitative urine and serum gonadotropins are indicated in order to pick

up early cases in which the titer of hormone may not be sufficient to give a positive pregnancy test.<sup>11</sup> It is stated<sup>12</sup> that certain other embryonal tumors of a less malignant character also produce increased amounts of gonadotropic hormone. After surgical or roentgen therapy, repeated gonadotropin assays are of use in following the course of the disease.

*Hydatid Mole and Chorionepithelioma.*—In hydatid mole, since it is a tumor of chorionic tissue, increased levels of gonadotropic hormone above what would be expected for the period of pregnancy are often encountered. Since this condition occurs early in pregnancy when the hormone level is normally high, a diagnosis of hydatid mole on the basis of a very high hormone level must be made with caution. The so-called "quantitative" pregnancy test may be particularly deceptive. It is doubtful that a positive Friedman test in a dilution of less than 1:500 can be considered significant in early pregnancy.

The presence of persistent high titers of gonadotropic hormone after delivery or an abortion raises suspicion of a chorionepithelioma. The hormone titer on quantitative assays rapidly increases, whereas if normal placental tissue has been retained the hormone level gradually falls.

*Pituitary Tumors.*—In the advanced stages of pituitary tumors of all types the gonadotropin excretion is generally diminished or absent. Occasionally in the early stages of an eosinophilic or basophilic adenoma, moderately increased values may be obtained.

## ESTROGENS

In the nonpregnant female estrogens are secreted primarily by the ovaries, chiefly by the follicular epithelium, but probably also by the granulosa, theca, interstitial and luteal cells. It is probable that  $\alpha$ -estradiol is the estrogen made by the ovary and this is in turn converted as a result of metabolic processes into estrone and estriol. All three of these "natural" estrogens may be recovered from the urine. There is also evidence that some estrogens are produced by the metabolic conversion of certain steroids of the adrenal cortex, and possibly, of the testis, which accounts for the estro-



gens found in the urine of postinvolutional women and men. During pregnancy large amounts of estrogens are also made by the placenta.

### Estrogen Determinations

Biologic assay still remains the most generally useful method for the determination of estrogens in biologic fluids. Some modification of the *Allen-Doisy test* is usually employed, in which the material or extract is injected into castrated adult mice or rats and various degrees of vaginal estrus are determined. Such tests are capable of detecting very minute amounts of estrogen. Unfortunately, however, wide degrees of variation are possible with even minor alterations in technic, so that results from different laboratories are not generally comparable and interpretation with respect to normal should be made by the particular laboratory.

In the blood of nonpregnant women sufficient hormone is present to be detected in certain stages of the menstrual cycle, either by injection of whole serum (Fluhmann test<sup>6</sup>) or blood extracts (Frank and Goldberger test, etc.). The estrogens in the urine are present chiefly in the conjugated state, therefore they must be freed by acid hydrolysis and then extracted with a steroid solvent, partially purified and then assayed.

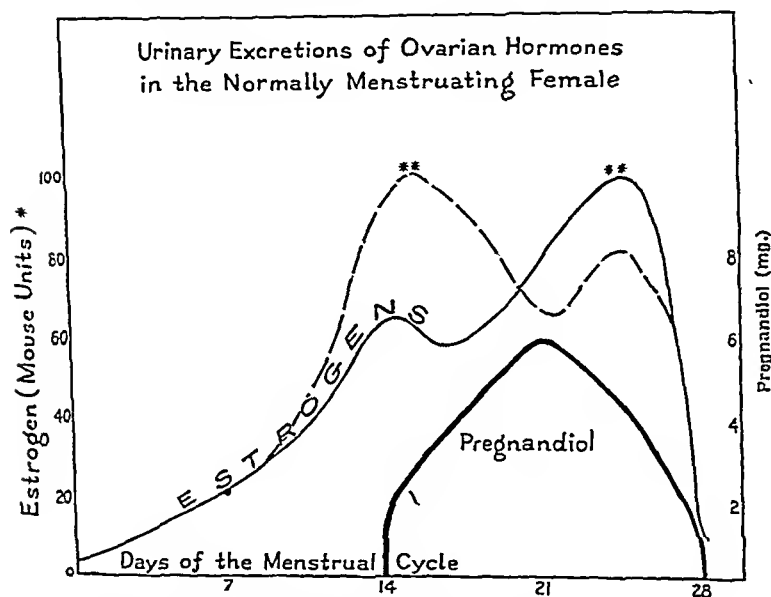
A number of colorimetric determinations for estrogens have appeared. At present these are useful only where relatively large amounts of the hormone are present as in pregnancy urine.

### Normal Estrogen Values

*Childhood.*—Even in very young children small amounts of estrogens are excreted in the urine.<sup>13</sup> After the age of eight there is an increase in the urinary estrogen of girls and as early as a year and a half before the menarche cyclic variations in the estrogens may be noted.

*Reproductive Period.*—In the normally menstruating female from puberty to the menopause there is a cyclic variation in estrogens (Fig. 238). From a low level at the onset of the flow the daily urinary excretion of estrogens rises to reach a peak at the midperiod, generally in association with the peak in gonadotropic excretion. This regresses slightly but then rises again during the period of increased corpus luteum function and reaches a second peak in the premenstrual phase, to be followed then by a rapid drop preceding the flow. In some instances the first peak may be higher than the second, but as a rule we have found the opposite to be more common. There is considerable variation in the shape and height of the curves in different individuals and from month to month in the same individual.

Similar findings may be found in the blood using whole serum (Fluhmann technic). With the Frank-Goldberger test usually the premenstrual peak can be demonstrated. For most purposes the blood estrogen studies are not as reliable as the urinary findings, since only a small amount of hormone is present in the amount of blood which can be conveniently taken. In some instances, however, determinations of both



\*This mouse unit approximately equivalent to 5 i. u.

\*\*Highest estrogen peak may be reached in mid-cycle or premenstrually

Fig. 238.

blood and urine estrogens are useful. During pregnancy the estrogen levels in the blood are sufficient to make direct assays of the serum a convenient and accurate method.

*Climacteric.*—The normal menopause is characterized by a decrease in estrogens and an increased excretion of gonadotropins. After the menarche the urinary estrogens generally fall to less than 13 mouse units each twenty-four hours.

*Pregnancy.*—During the first two months of gestation there

is a slow increase in the estrogen content of the blood and urine. At twelve weeks the level is definitely higher than is likely to be encountered in any other state, and although certain pregnancy tests have been based on this finding the much earlier and much greater increase in gonadotropins serves as a more useful criterion. The estrogens continue to rise regularly to reach their highest peak at or near the onset of labor (Fig. 237). Some workers believe that there is a moderate fall in estrogens several weeks before the end of gestation. Also in certain patients with toxemias of late pregnancy there is a decrease in blood and urinary estrogens, generally associated with an increase in gonadotropin titers.

#### Estrogen Determinations for Clinical Diagnosis

*Precocious Puberty.*—In true precocious menarche gonadotropin and estrogen levels similar to those of the normal menstrual cycle occur along with all the attendant normal physiologic processes of puberty. These cases must be differentiated from pseudo pubertas praecox due to various new growths.

*Functional Menstrual and Ovarian Disturbances.*—Amenorrhea.—Several patterns of hormone excretion have been found in patients with primary or secondary amenorrhea:<sup>14, 15</sup> (1) A consistently low estrogen excretion with normal or increased gonadotropins, which occurs in primary ovarian deficiency. (2) A group in which diminished levels of estrogen are associated with absent or diminished titers of gonadotropins. Here the defect is primarily a pituitary deficiency. (3) Normal levels of estrogens associated with normal gonadotropin excretion. Here some disturbances in the ratio between estrogens and progesterone or androgens may exist. (4) Consistently high levels of estrogen with no definite cycling apparent. Such findings have been reported in the presence of cystic ovaries, and some cases of hypothyroidism and adrenal cortical hyperfunction.

*Functional Uterine Bleeding.*—The etiology of functional uterine bleeding is often obscure and undoubtedly many factors may be responsible, both of an endocrine nature and in certain abnormalities<sup>16</sup> of local origin. Of those associated

with abnormal hormone findings two groups deserve mention: (1) A group with normal or high excretion levels of gonadotropins and estrogens. Frequently these patients have endometrial hyperplasia. (2) Those with low levels of estrogens and absent pregnandiol excretion. In these patients bleeding from an atrophic endometrium occurs. In addition, many other abnormal patterns of hormone excretion have been found in individual cases, indicating that many types of sex-endocrine dysfunction can produce this symptom. Although the underlying factors may remain obscure even after repeated hormone assays, the latter afford us at the present our best objective guide to logical therapy.

**Dysmenorrhea.**—Dysmenorrhea is a symptom which can result from a great many causes; not infrequently an endocrine factor is responsible. As in the case of functional bleeding, several types of sex-endocrine dysfunction have been found. The commonest combination in our experience is a diminution in both gonadotropins and estrogens, clinically often associated with a hypoplastic uterus.

**Ovarian Tumors.**—High blood and urine estrogen levels have been found in granulosa cell tumors of the ovaries.<sup>17</sup> Although the estrogen values associated with these tumors are generally definitely increased, they usually are not high enough to approach the levels of the last trimester of pregnancy. We have recently observed a child with an adrenal-rest tumor of the ovary in whom there was a moderate increase in estrogens, but a much more marked increase in androgens and 17-ketosteroids. Ovarian cysts and other ovarian tumors are not usually associated with significantly increased amounts of estrogens.<sup>18</sup> There is reason to suspect, however, that in certain individuals excessive or prolonged gonadotropic stimulation may be a factor in the production of ovarian cysts.

**Adrenal Cortical Tumors.**—In certain tumors and hyperplasias of the adrenal cortex associated with the adrenogenital syndrome increased amounts of estrogens may sometimes occur.<sup>19, 20</sup> There is usually, however, a more striking increase in the androgens and 17-ketosteroids. Very high values of estrogens have been considered by Frank as char-

acteristic of cortical carcinoma.<sup>21</sup> However, as pointed out by Wintersteiner, by no means all cases of cortical carcinoma have exhibited this feature, so that only a strongly positive test may be regarded as diagnostically significant.

*Other Tumors.*—In view of the demonstrated carcinogenic action of various estrogens in lower animals, many studies have been made of the estrogen excretion associated with various types of benign and malignant tumors, particularly of the uterus, cervix and breast.

*Mastalgia and Chronic Cystic Mastitis.*—Unquestionably, many instances of these conditions are associated with abnormalities in menstruation and ovarian function and often with abnormal patterns of estrogen and pregnandiol excretion.<sup>22</sup> In a number of cases, definite hyperestrogenism has been found, in others a relative hyperestrogenism has been postulated because of a corpus luteum deficiency. It is difficult, however, at the present time to draw any general conclusions on an underlying endocrine mechanism, since no consistent abnormal pattern has been demonstrated. At the present time the best that can be done is to approach each case individually and attempt to correlate the condition from the individual findings.

### PROGESTERONE

Progesterone is a steroid hormone secreted by the corpus luteum which has the specific function of preparing the uterus for the reception and nutrition of the embryo. Progesterone is responsible for the secretory changes which characterize the typical premenstrual endometrium. It also serves to diminish the spontaneous contractions of the uterus. During the first trimester of gestation it is believed that progesterone is made chiefly by the corpus luteum of pregnancy, but that thereafter the placenta takes over this function.

#### Methods of Assay

It was demonstrated by Venning and Browne<sup>23</sup> that progesterone is excreted in the urine as pregnandiol and conjugated with glycuronic acid to form a water-soluble compound, sodium pregnandiol glycuronate. Although pregnandiol has no biologic activity its amount in the urine may be determined gravimetrically by a chemical procedure which is not

too complex for limited chemical use. The amount of pregnandiol in the urine serves as a measure of corpus luteum activity.

Where large amounts of progesterone are present in the blood, as during pregnancy, the hormone may be demonstrated by biologic assay.<sup>24</sup>

### Normal Values

Pregnandiol is not normally found in the urine of children or men.

In the normally menstruating female pregnandiol appears quite suddenly in the urine about twelve or thirteen days before the onset of menstruation, that is, shortly after ovulation. The daily amount in the urine is quite variable but generally ranges from 3 to 6 mg. (Fig. 4). The excretion usually reaches a peak about the twenty-first day of the cycle and then drops abruptly two or three days before the onset of bleeding. The curve of pregnandiol excretion thus closely parallels the rise, activity and retrogression of the corpus luteum.<sup>25</sup> During pregnancy the pregnandiol excretion increases only slightly until about the tenth to twelve week and then continues to rise further to reach a peak of 60 to 100 mg. daily at term.<sup>26, 27</sup> At the time of the onset of labor a falling rate of excretion may be encountered.<sup>28</sup>

### Pregnandiol Determinations for Clinical Diagnosis

*Functional Menstrual and Ovarian Disorders.*—In non-pregnant women the demonstration of normal amounts of pregnandiol during the latter half of the cycle constitutes evidence in favor of the presence of a normally functioning corpus luteum. It also indicates the probability that ovulation has occurred, although this is still open to some question. In following sterility patients in whom some defect in ovulation is suspected it is well to correlate the pregnandiol findings with endometrial biopsies and vaginal smears.

It has already been indicated that in some instances of functional uterine bleeding and dysmenorrhea absent or inadequate corpus luteum activity may be an etiologic factor. In such instances pregnandiol determinations during the latter half of the cycle may be of diagnostic value.

*Habitual and Threatened Abortions.*—The great majority of spontaneous abortions occur from the eighth to twelfth

weeks during the period when it is believed that the placenta is taking over the function of the corpus luteum of pregnancy. Since the production of normal amounts of progesterone is believed to be essential for the continuation of gestation, it is suspected that premature failure of the corpus luteum of pregnancy or inadequate placental secretion of progesterone may be the etiologic factor in many spontaneous abortions. Frequent pregnandiol determinations in patients with a history of habitual abortion may prove worth while in establishing an etiologic diagnosis and in guiding therapy.<sup>26</sup>

*Toxemias of Pregnancy.*—There are several reports<sup>27, 28</sup> indicating that in the true "toxemias" of late pregnancy there is a progestin deficiency; this may have particular bearing on the increased estrogens and high gonadotropins commonly found in these patients.

*Adrenal Cortical Hyperfunction.*—There have been a number of reports recently of the occurrence of pregnandiol in the urine in conditions associated with adrenal cortical tumors or hyperplasia. These include patients with an adrenogenital syndrome,<sup>31</sup> pseudohermaphroditism,<sup>32</sup> and Cushing's syndrome.<sup>33</sup>

## ANDROGENS

The testis hormone, which is probably testosterone, is secreted by the interstitial cells of Leydig under the influence of pituitary gonadotropic stimulation and is excreted in the urine as a number of related steroid compounds some of which have androgenic properties, particularly androsterone and dehydroandrosterone, and others which are biologically inactive.

Sufficient evidence has accumulated to indicate that a part of the androgens normally excreted is derived from an extragonadal source. There is some difference of opinion as to whether the ovary is also capable of producing androgens.

### Methods of Assay

The most commonly employed methods for the determination of androgens are based upon the stimulation of comb-growth in the capon and baby chick or growth of seminal vesicles or prostate of the castrated

rodent. It will be readily admitted that the methods available for clinical purposes are far from the ideal. The *capon test*, which is the most accurate, is time-consuming and expensive and impracticable for general clinical use. The *baby chick test* is capable of great variations unless very carefully controlled, while the *seminal vesicle test* may be influenced by other substances in the extract.

For clinical purposes we have found the baby chick test<sup>33</sup> to be the most satisfactory for our purpose. Gross errors can be eliminated if each extract is tested at three different levels along with three different androsterone control levels. By direct application of ether extracts to the comb very small amounts of androgenic activity can be demonstrated. Many modifications of the baby chick test have been reported.

Recently certain *chemical tests* have come into use which are proving to be very useful. At the present time, however, these tests do not distinguish between the biologically active and inactive androgens (see section on 17-ketosteroids).

### Normal Values

*Childhood.*—Very small amounts (from 0.3 to 2 milliequivalents of androsterone)<sup>34</sup> of androgenic activity may be demonstrated in urine extracts of children of both sexes. A very distinct rise may be found in boys soon after the age of eight which then gradually increases to the adult male level soon after puberty.

*Reproductive Period.*—Male.—When tested by the capon method the normal male excretes about the equivalent of 7 mg. (70 international units) of androsterone each twenty-four hours.<sup>35</sup> Fluctuations of from 40 to 100 international units are not uncommon, but no definite cyclic variation is usually present.

Female.—It is a well known fact that the female normally excretes almost as much androgens as the male, the values generally ranging from about the equivalent of 30 to 80 international units of androsterone with the average value of about 50 international units. Clinical evidence at present indicates that in the female the androgenic activity is probably derived primarily from the adrenal cortex, although some part may also be derived from the ovaries. Although there are occasional reports of cyclic variations in androgens in the female, the present consensus is that despite considerable day-to-day variation there is no definite pattern of androgen excretion.<sup>36</sup>

*Pregnancy.*—During normal pregnancy the androgen values



generally fall within the range for the normal nonpregnant female.

*Climacteric.*—In males past the age of fifty it is not uncommon to find diminished titers of androgens. In females, on the other hand, the androgen values are generally normal or may be moderately increased.<sup>37</sup>

#### Androgen Assays for Clinical Diagnosis

*Hypogonadism.*—The finding of consistently low values of urinary androgens in males aids in establishing the diagnosis of hypogonadism. When such findings are associated with high gonadotropin values primary testicular failure may be presumed, whereas absence of gonadotropic hormone favors primary pituitary hypofunction.

*Ovarian Dysfunction.*—Androgen values are usually not appreciably altered in most functional disturbances of the ovaries. It is of interest that in most instances of hypoovarianism the androgens are normal and sometimes increased,<sup>37</sup> thus resulting in a definite increase in the androgen-estrogen ratio. It is possible this may account for the hirsutism and other mild evidences of virilism which many of these patients show.

*Masculinizing Syndromes.*—Increased levels of androgenic activity in the urine are encountered in association with most masculinizing tumors, such as carcinoma of the adrenal cortex, arrhenoblastoma of the ovary and adrenal cortical tumors of the ovary. In Cushing's syndrome the largest amounts of androgens are found in those cases in which an adrenal tumor is present, but increased values may also occur if marked hyperplasia of the adrenal cortex is present.<sup>20</sup> In many instances in which marked hypertrichosis is present without changes in the adrenals the androgen values are usually within normal.

#### 17-KETOSTEROIDS

This is a colorimetric test made on urine extracts which in the male serves as an index of the combined activity of the adrenal cortex and the testis, and in the female chiefly of the adrenal cortex. The reaction is used for the detection of

those steroids which have a ketone group on the 17th carbon atom (17-ketosteroids). It is based upon the color reaction introduced by Zimmerman.<sup>38</sup>

It is to be pointed out that the 17-ketosteroids are not entirely equivalent to androgen assays since some steroids which are not androgenic give the reaction while some androgens are not 17-ketosteroids and do not react. Also, estrone is a ketosteroid but since this is weakly phenolic it may be removed by washing with alkali during the extraction process.

The nonphenolic 17-ketosteroids which have been found in human urine are as follows:<sup>39</sup> androsterone, aetiocholan-17-one-3-ol and dehydro-iso-androsterone. Several other compounds have been isolated from the urine of patients with adrenal hyperplasia, adrenal tumors and testicular tumors.

### Normal Values

The normal range varies somewhat with the modifications in the technic employed.

*Childhood.*—Children excrete small amounts of 17-ketosteroids, the amounts generally ranging from less than 1 to 5 mg. equivalents of androsterone each twenty-four hours.

*Reproductive Period.*—Females.—The usual range in the normal female is from 5 to 15 mg. equivalents of androsterone each twenty-four hours. Considerable day-to-day variations are present but these bear no definite correlation to the menstrual cycle.

*Males.*—The average values in the male are slightly higher than in the female. The usual normal range is from 8 to 20 mg. equivalents of androsterone.

*Climacteric.*—In menopausal women the 17-ketosteroids tend to be moderately increased, probably due to adrenal cortical hyperfunction.<sup>40</sup>

In males past the age of fifty the 17-ketosteroids are normal or low.

### 17-Ketosteroids in Clinical Diagnosis

A sufficient number of reports have appeared to make it apparent that 17-ketosteroid determinations are a useful endocrine diagnostic procedure. The results, however, must be interpreted with caution, since they apparently may be influenced by certain nonendocrine conditions. Thus low values have been reported in malnutrition, various gastrointestinal diseases, anemia, infection and liver diseases.<sup>39</sup>

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obtained.<sup>38</sup> It is suggested that this test may help in separating such patients from those with anorexia nervosa in which the values may be normal or moderately low.

*Hypothyroidism.*—Very low values are obtained in patients with hypothyroidism,<sup>39</sup> even when under thyroid therapy.<sup>43</sup>

*Eunuchoidism.*—Low values are obtained in those cases of male hypogonadism associated with panhypopituitary function. They are slightly decreased in those due to primary gonadal hypofunction and moderately low in those with hypogonadotropic function.<sup>39</sup>

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*Adrenal Cortical Hypofunction.*—Very low or absent values are found in Addison's disease. The lowest values are generally obtained in female patients.<sup>39</sup>

*In Masculinizing Syndromes.*—In patients with an adrenogenital syndrome due to an adrenal tumor or adrenal hyperplasia the 17-ketosteroid values are high.<sup>39</sup> In patients with Cushing's disease high values are also encountered. The highest values, however, occur in those with adrenal carcinomas.

In simple hirsutism the values may range from normal to moderately increased titers. Recent studies<sup>41</sup> indicate that further fractionation of the urinary steroids may serve as a basis of differentiation of these cases.

Fraser and his associates found that in a patient with virilism due to an arrhenoblastoma the 17-ketosteroid assay was within normal limits as well as in a patient with virilism due to a disgerminoma. We have encountered high values in a child with a masculinizing syndrome due to an adrenal rest tumor of the ovary.

*Menstrual and Ovarian Disturbances.*—The present data do not indicate that 17-ketosteroid values will be of much diagnostic aid in the more common gynecologic disorders caused by disturbances in the pituitary-ovarian cycle. In a study of a number of such disorders Hamblen, Cuyler and Baptist<sup>40</sup> noted the following results: In amenorrheic patients normal values were obtained in those with delayed menarche while definite increases occurred in those with intercurrent amenorrhea. In women with ovarian failure those in the premenopausal group excreted increased amounts of 17-ketosteroids, while soon after ovarian failure due to oophorectomy or physiologic causes, increased titers of 17-ketosteroids are found; after a variable number of years these tend to return to normal. These data are held to support the thesis that intercurrent or adult estrogenic ovarian failure is followed by adrenal hyperactivity. In menometrorrhagia related to simple corpus luteum failure normal values were found.<sup>42</sup>

*Acromegaly.*—The 17-ketosteroid values are normal or low in this condition<sup>39</sup> despite the adrenal cortical hypertrophy.

*Hypopituitarism.*—In patients with pituitary panhypopituitarism due to various causes zero or very low values are

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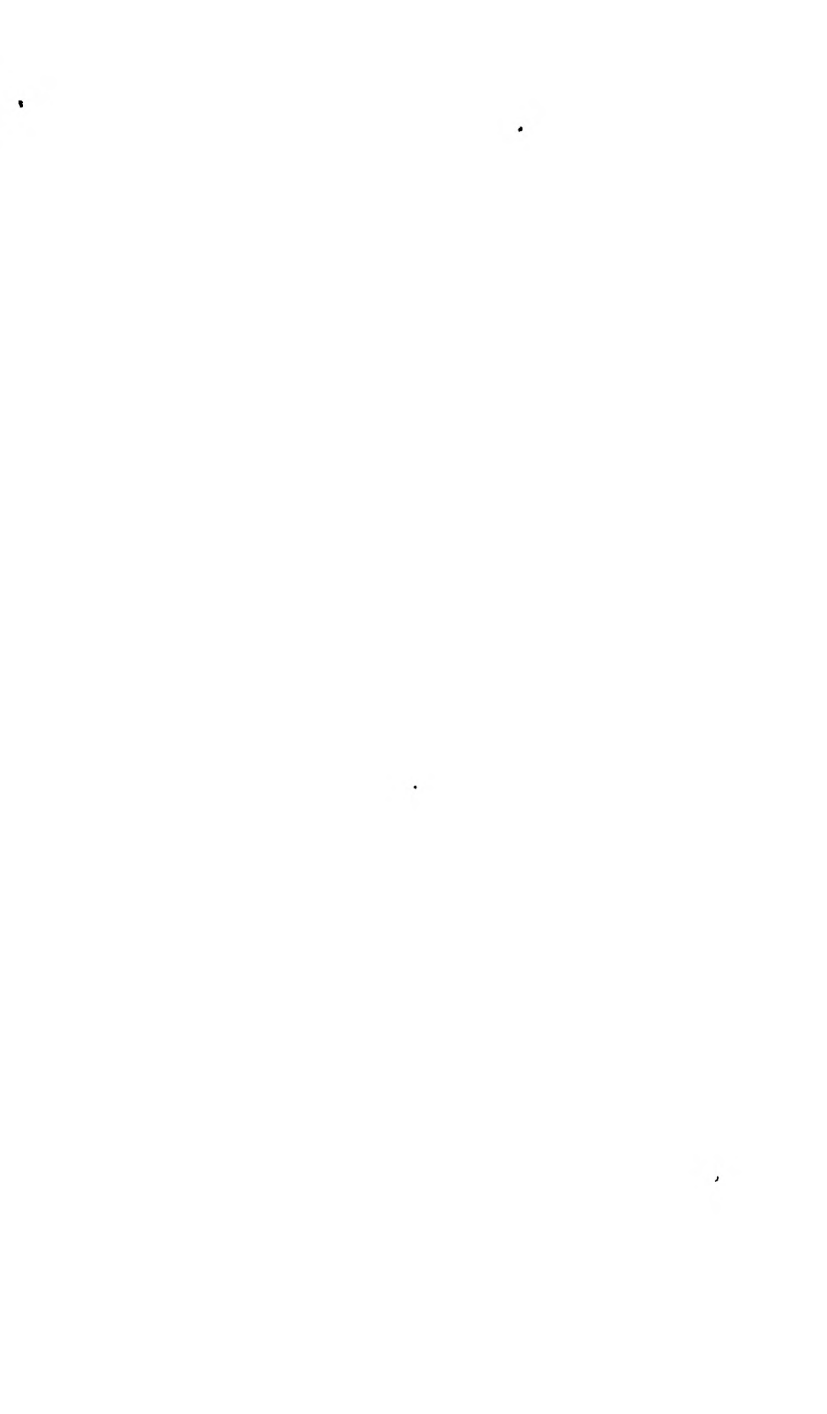
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